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Early life course determinants of psychopathology

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Abstract

Background: Mental health problems are associated with a range of adverse outcomes as well as increased risk of later morbidity and premature mortality. Help seeking is uncommon at the early stages of mental health problems. Rather, treatment is often sought by patients after illnesses have already caused considerable distress or had substantial adverse personal, social and economic impacts. The purpose of the current work is to investigate the role of a number of early life course risk factors in the development of later psychopathology, using advanced statistical and epidemiological approaches applied to longitudinal data to ascertain predictive and causal pathways. The overall scope of this thesis is to provide the evidence necessary for developing primary and secondary prevention programs aimed at reducing the burden of mental illness on society.

Aim 1: To investigate the role of intrauterine growth restriction in increasing the risk of psychiatric disorders characterised by negative affectivity.

Aim 2: To investigate the potential for a transmission of maternal psychopathology to offspring.

Aim 3: To assess whether maternal prenatal infection and exposure to stressful life events predict positive psychotic experiences in the offspring directly, or indirectly via postnatal risks and antecedents of psychosis.

Aim 4: To investigate potential risk factors for the increased rates of female post-traumatic stress disorders, including gender-specific vulnerability resulting from physical assault and cognitive ability.

Methods: The data came from the Mater University Study of Pregnancy (MUSP), a prospective pre-birth cohort study which began in 1981 at the Mater Hospital in Brisbane, Australia. The baseline sample consisted of 7,223 pregnant women attending their first obstetric visit for that pregnancy. Since then follow-ups over 21 years have prospectively ascertained a range of health related data on both mother and child. The current work uses predictor variables and covariates from every measurement period, and behaviour and mental health measures ascertained from the offspring at ages 14 and 21 years. A number of statistical and methodological approaches were applied to estimate the longitudinal association between a number of early life course risk factors and later psychopathology, and to account for attrition.

Key findings: The relationship between birth weight and later psychopathology was specific to particular psychiatric diagnoses, namely Post-Traumatic Stress Disorders, and comorbid Major Depression and Generalised Anxiety Disorders. The combination of maternal prenatal depressive, anxious and stress symptoms predicted increased internalising and externalising behaviour problems in adolescent and adult offspring. Prenatal maternal infections and stressful life events predicted later offspring psychotic experiences via the intermediaries of early infant illness

susceptibility and child behaviour problems respectively. The risk of Post-Traumatic Stress Disorder associated with physical assault and lower cognitive ability was greater in females. **Conclusions**: The current work contributes a number of substantive findings to the existing body of work related to early life course determinants of psychopathology, using sophisticated statistical techniques applied to epidemiological methods to clarify relationships, and strengthens evidence for preventive approaches to psychopathology

Declaration by author

This thesis **is composed of my original work, and contains** no material previously published or written by another person except where due reference has been made in the text. I have clearly stated the contribution by others to jointly-authored works that I have included in my thesis.

I have clearly stated the contribution of others to my thesis as a whole, including statistical assistance, survey design, data analysis, significant technical procedures, professional editorial advice, and any other original research work used or reported in my thesis. The content of my thesis is the result of work I have carried out since the commencement of my research higher degree candidature and does not include a substantial part of work that has been submitted **to qualify for the award of any** other degree or diploma in any university or other tertiary institution. I have clearly stated which parts of my thesis, if any, have been submitted to qualify for another award.

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Publications during candidature

Peer reviewed journal articles

1. **Betts, K. S**., Williams, G. M., Najman, J. M. & Alati, R. (2011). The association between birth weight and anxiety disorders in young adults. *J Anxiety Disord* 25, 1060-7.

2. **Betts, K. S**., Williams, G. M., Najman, J. M., Scott, J. & Alati, R. (2013). The association between lower birth weight and comorbid generalised anxiety and major depressive disorder. *Journal of affective disorders* 146, 231-7.

3. **Betts, K. S.,** Williams, G. M., Najman, J. M. & Alati, R. (2014). Maternal depressive, anxious, and stress symptoms during pregnancy predict internalizing problems in adolescence. *Depression and Anxiety* 31, 9-18.

4. **Betts, K. S**., Williams, G. M., Najman, J. M. & Alati, R. (2014). The relationship between maternal depressive, anxious, and stress symptoms during pregnancy and adult offspring behavioral and emotional problems. Depression and anxiety.

5. **Betts, K. S.,** Williams, G. M., Najman, J. M., Scott, J. & Alati, R. (in press). Maternal prenatal infection, early susceptibility to illness and adult psychotic experiences: a birth cohort study. *Schizophrenia Research* 3/04/2014.

6. **Betts, K. S.,** Williams, G. M., Najman, J. M., Scott, J. & Alati, R. (2014). Exposure to stressful life events during pregnancy predicts psychotic experiences via behaviour problems in childhood. *Journal of psychiatric research* **59**, 132-139.

7. **Betts, K. S**., Williams, G. M., Najman, J. M., Bor, W. & Alati, R. (2012). Pre-trauma verbal ability at five years of age and the risk of post-traumatic stress disorder in adult males and females. *Journal of Psychiatric Research* 46, 933-939.

8. **Betts, K. S**., Williams, G. M., Najman, J. M. & Alati, R. (2013). Exploring the female specific risk to partial and full PTSD following physical assault. *Journal of Traumatic Stress* 26, 86-93.

9. **Betts, K. S**., Williams, G. M., Najman, J. M. & Alati, R. (2013). The role of sleep disturbance in the relationship between post-traumatic stress disorder and suicidal ideation. *Journal of anxiety disorders* 27, 735-41.

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13. Liddle, K., Askew, D., **Betts, K. S**., Hayman, N. & Alati, R. (in press). Predictors of specialist referral for developmental and behavioural problems in a Queensland urban Indigenous community: a cross-sectional study. *Australian Family Physician* 31/3/2014.

14. Alati, R., Baker, P., **Betts, K. S**., Connor, J. P., Little, K., Sanson, A. & Olsson, C. A. (2014). The role of parental alcohol use, parental discipline and antisocial behaviour on adolescent drinking trajectories. *Drug and alcohol dependence* 134, 178-84.

15. Salom, C. L., **Betts, K. S.,** Williams, G. M., Najman, J. M., Scott, J. & Alati, R. (in press). Do young people with comorbid mental and alcohol disorders experience worse behavioural problems? *Psychiatry Research* 20/5/2014.

Book chapters

16. **Betts, K. S**., & Alati, R. The importance of comorbidity to suicide risk in Post-Traumatic Stress Disorders. In Martin, C., Preedy, V. R. & Patel, V. B. (2014). Comprehensive Guide to Post-Traumatic Stress Disorders. London, Springer Reference. (Submitted)

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Publications included in this thesis

1. **Betts, K. S**., Williams, G. M., Najman, J. M. & Alati, R. (2011). The association between birth weight and anxiety disorders in young adults. *J Anxiety Disord* 25, 1060-7.

2. **Betts, K. S**., Williams, G. M., Najman, J. M., Scott, J. & Alati, R. (2013). The association between lower birth weight and comorbid generalised anxiety and major depressive disorder. *Journal of affective disorders* 146, 231-7.

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Contributor	Statement of contribution
Betts, K.S. (Candidate)	Conceived the research question (100%) Designed the analysis (80%) Interpreted results (70%) Wrote the paper (100%)
Alati, R. (Primary supervisor)	Edited papers (80%)
Williams, G.M. (Secondary supervisor)	Designed the analysis (20%) Interpreted results (30%)
Najman, J.M.	Edited papers (20%)
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Note: Each contributor played similar roles on each paper they were involved with, thus the contributions outlined above stand for each paper a contributor was involved with.

Contributions by others to the thesis

The contribution of others to this thesis is detailed in the above section concerning co-author contribution to published journal articles.

Statement of parts of the thesis submitted to qualify for the award of another degree

No part of this thesis was submitted to qualify for the award of another degree.

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Table of Contents

List of Tables

List of Abbreviations

ATAPS	Access to Allied Psychological Services
CBCL	Child Behaviour Checklist
CES-D	Centers for Epidemiologic Studies – Depression
CFA	Confirmatory factor Analysis
CIDI	Composite International Diagnostic Interview
CNS	Central Nervous System
DOHaD	Developmental Origins of Health and Disease
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSSI	Delusions-States-Symptoms Inventory
EFA	Exploratory Factor Analysis
GA	Gestational Age
GAD	Generalised Anxiety Disorders
GC	Glucocorticoids
HPA	Hypothalamic-pituitary-adrenal (axis)
ICD	International Classifications of Diseases
IQ	Intelligence Quotient
IUGR	Intrauterine Growth Restriction
LCGA	Latent Class Growth Analysis
LFU	Loss to Follow-Up
MDD	Major Depressive Disorders
MMH	Mater Misericordiae Hospital
MUSP	Mater University Study of Pregnancy
PD	Panic Disorders
PPVT-R	Peabody Picture Vocabulary Test - Revised
PTSD	Post-Traumatic Stress Disorders
SEM	Structural Equation Modelling
SES	Socioeconomic Status
SGA	Small for Gestational Age
SRRS	Social Readjustment Rating Scale
YASR	Young Adult Self-Report
YSR	Youth Self Report

Chapter 1 - Purpose of the current work

Mental disorders and the unrealised potential of primary prevention

Affective and anxiety disorders are very common among Australians, having prevalence rates of 6.2% and 14.4% respectively (1, 2), and accounting for 6.2 and 4.4 days out of role per 30 days for those diagnosed with a 12 month disorder (1). Psychotic disorders are comparatively rarer in the general population, with the prevalence of schizophrenia and bipolar disorders estimated to be 0.46% and 2.5% respectively (3, 4). However, the societal cost of psychotic disorders are disproportionately large because symptoms are severe, persistent, and usually begin in adolescence and early adulthood resulting in a lasting impact on the individual's economic opportunities and contribution (3).

Despite some worthwhile initiatives, including the Access to Allied Psychological Services (ATAPS) and Better Access programs (5, 6), the majority of people with affective or anxiety disorder do not seek treatment, and for those who do, the effectiveness of these treatments remains largely unknown (7). Outcomes among those receiving treatment for the less prevalent psychotic disorders is poor, with one third having persistent symptoms, and some even experiencing increased levels of impairment (8). Preventing these disorders before they become chronic would largely reduce their burden (9). In order to develop successful mental health prevention programs, policy makers need to know the pathways leading to the development of mental health problems, and such primary prevention approaches are likely to gain greater acceptance if evidence can robustly link specific life-course factors with later mental illness (10).

The role of life course epidemiology in the prevention of mental disorders

Life course epidemiology can provide information on early life risk factors for later mental disorders which are amenable to intervention. Though causation cannot be explicitly demonstrated in observational epidemiological studies, many programs aimed at preventing physical illness have had their success judged empirically (10). If multiple lines of evidence show that early life risk factors are strongly linked to later mental illness, then studies which randomise the prevention efforts could assess the importance of the empirical relationship. The latest National Mental Health Plan 2009-2014 includes a focus on prevention of childhood trauma and abuse (11), and for over a decade programs have been in place to detect and treat maternal prenatal and perinatal depression (12). However, a range of other early life risk factors have been identified through epidemiological studies as potentially influential to later mental illness, but for which further research is needed.

Chapters 2 and 3 discuss how life course epidemiology provides a framework for studying disease development across time by drawing on knowledge from a number of scientific disciplines and making use of the latest advances in longitudinal statistical analyses (13). The studies undertaken over the course of this doctorate explore a range of mental health disorders and early life course risk factors, all linked by a common theme: the application of life course epidemiological methods to better elucidate the role of these early life risk factors.

The role of epidemiology in psychiatric nosology

As a scientific discipline, epidemiology is well placed to provide information regarding how we define the medical conditions under our study, thereby making a direct and ongoing contribution to matters of psychiatric nosology separately to the basic sciences. This is a direct consequence of the nature of our current understanding of psychiatric disorders. It is

true that all medical conditions are defined upon some level of abstraction, ranging from incompletely understood biological agents to a deviance from a physiological norm, for which population level statistical data have in some instances clearly contributed. However, psychiatric disorders are among the more abstract of medical conditions and are in many cases understood only as a set of indicators which do not reflect a single, clear concept (14).

Advanced statistical methods (discussed in chapter 3) using data from large samples of general populations provide an empirical solution to determining the structure of mental disorders, and may have certain advantages over solely relying on clinical definitions (15). These advantages include; (i) refining the definition of the psychiatric disorders under study so to better associate the disorder to an etiological factor by reducing the misclassification inherent when employing a binary diagnostic definition; (ii) and identifying the significance of sub-clinical expressions of the disorders to the individual and society. Although in practice the current work regularly employs the standard DSM definitions as the outcome variables, where appropriate there has been a conscious effort to not simply take the DSM definitions for granted. In this way the current work attempted to strike a balance between two competing approaches, one which emphasises the practical and pragmatic search for risk factors relevant to sufferers of the current day, the other which emphasises the need for more theoretical information relevant to the epistemic iteration process by which scientific knowledge is continually updated and applied to our approximation of reality (16).

Thesis outline

Chapter one frames the purpose of the current work philosophically by outlining the role of life course epidemiology in better generating evidence for mental health prevention strategies. Chapter two begins by introducing frameworks within which to understand the development of health and disease throughout the life course. This section begins with a

strong focus on the Developmental Origins of Health and Disease (DOHaD) to inform investigations into prenatal risk factors, before outlining how a biopsychosocial framework can be applied to investigations of risks operating in childhood and adolescence. In subsequent sections the main psychiatric disorders and behavioural problems are examined, then a review of the relationships under study is given. While the current work has limited capacity to contribute to knowledge of the mechanisms underpinning the associations, the biological and psychological mechanisms are briefly described in this chapter for three reasons: (i) to explain what may underlie the epidemiological associations, (ii) to illustrate that research into the mechanisms is in its infancy and prevention efforts cannot wait for such processes to be fully understood, (iii) and because evidence from the basic sciences often supports the specific findings.

Chapter three provides a detailed description of the Mater University Study of Pregnancy or MUSP and statistical methodologies employed. In addition, recent advances in statistical techniques are outlined and their application in the current work made explicit. Chapters 4 to 7 contain published and submitted manuscripts, with each chapter containing two manuscripts exploring the following: fetal development and psychopathology (chapter four), non-genomic transference of maternal psychopathology to offspring (chapter 5), prenatal risk factors for psychotic experiences (chapter 6), and gender-specific responses to traumatic stress (chapter 7). Chapter 8 reviews the main results of the papers and discusses the findings in relation to the strengths, limitations, future research, and implications for prevention, before providing a conclusion. It is worth noting that each paper also contains a literature review, methods section and discussion, meaning that despite efforts to reduce repetitious materials, some redundancy between the main document and the self-contained papers was inevitable.

Chapter 2 - Literature Review

Theoretical frameworks for disease development over the life course

The current work employs two main and somewhat overlapping frameworks when investigating life course risk factors for psychopathological outcomes in adolescence and early adulthood. The earliest life course risk factors, those occurring in prenatal and very early postnatal life, are explained in relation to the Developmental Origins of Health and Disease (DOHaD). On the other hand, risks which are more proximal to the outcomes, those occurring in childhood and adolescence, are explained in relation to the biopsychosocial model of disease development.

The DOHaD hypothesis originated from the work of David Barker, who used retrospective cohort studies to demonstrate a clear link between *lower* birth weight and a number of adult diseases in humans (17) including diabetes type 2, high blood pressure and cardiovascular disease (18-22). Later studies supported Barker's work, finding association between various proxy measures of Intrauterine Growth Restriction (IUGR) with similar indicators of physiological disease in adults (23-28). Here, differences in fetal growth are believed to result in part from the process of phenotype plasticity. Phenotype plasticity is central to the DOHaD hypothesis and refers to the process by which a particular genotype can develop into a number of different phenotypes during a stage of developmental plasticity by responding to environmental factors such as nutrient supply (17, 29). For humans, a critical period of developmental plasticity occurs *in utero* and is generally referred to as prenatal programming (17).

The relevance of this process to later non-communicable disease risk was conceptualized well by Van den Bergh as - "…the physiological, neuroendocrine or metabolic

adaptations that enable the fetus to adapt to changes in the early life result in a permanent programming (or re-programming) of the developmental pattern of proliferation and differentiation events within key tissues and organ systems and can have pathological consequences in later life" (30). A good illustration of how altered fetal development in response to maternal prenatal nutrient restriction can affect later disease risk is exemplified by the Dutch Famine Study. This study compared the health outcomes between adults who were exposed to the World War II famine (lasting between 5 to 6 months) at different stages of gestation, with those born just before, and conceived just after, the famine (31). Results showed that exposure to the famine in early gestation predicted higher rates of obesity in women aged 50 (32), exposure in mid- and late-gestation predicted decreased glucose tolerance (33), and higher rates of obesity were found among 19 year old males exposed to the famine during the first half of pregnancy (34).

The evidence resulting from the Dutch Famine Study demonstrated that the maternal environment is likely to impact on the fetus by programming its development to better suit it for the environmental conditions the mother encounters while pregnant. More specifically, if the mother's environment is undernourished, the fetus will develop in phenotype accordingly, that being, small in size with altered metabolic functioning, in preparation for a low caloric life-style once born. When nutritional conditions in extrauterine life do not match those for which were adapted during fetal development, the result may be the occurrence of one or more of the chronic diseases mentioned above, as the permanent programming puts the individual at odds with his or her environment (29). Using diabetes as an example, when the body's ability to metabolise glucose was set in a nutritionally deprived environment, the excess glucose available in later life due to changing environmental conditions may lead to diabetes, as the body is unable to adjust to these excesses (21).

These findings are supported by biological evidence from animal models. Experimentally induced nutrient restriction during pregnancy is linked with increased blood pressure, glucose intolerance, insulin resistance and obesity in rodents and sheep, and these associations are accompanied by tissue remodelling in key organs (35). Further, the programming effect of nutrient restriction on aspects of metabolic syndrome in rodent offspring has been found to become stronger as age advances (36), supporting the notion that developmental plasticity decreases with age while risk of illness increases as the maladaptive systems set down over early development succumb to cumulative environmental exposures (37). Growing evidence suggests that epigenetic mechanisms may underlie reprogramming effects, with nutrient restriction found to impact the expression and promoter methylation of PPAR-α in the liver (38). While epigenetic and physiological changes have not generally been simultaneously assessed within the same study, animal models which induce programmed hypertension and obesity have documented a range of epigenetic changes (39, 40). Prenatal nutrient restriction has also been found to predict DNA methylation of selected loci in human offspring (41), but how epigenetic mechanisms interact with environmental exposures remains unknown as relevant studies in humans are lacking.

Infancy and childhood are marked by rapid growth and therefore also represent sensitive periods in which irreversible alterations in development, which may have consequences for later disease risk, are made to suit environmental conditions (37). The biopsychosocial model may offer a more comprehensive framework than the DOHaD framework to study risk factors operating in childhood and adolescence which impact on later psychopathological outcomes (42). An example of this is the relationship between exposure to a traumatic situation and the stress directly resulting from such a situation, a phenomenon now formalised as PTSD. Though the relationship seems clear at first,

numerous biological, psychological and social factors appear to play a role in determining why the same traumatic event impacts psychopathology across individuals differently (43, 44). Though criticized for its broad approach (45), if used to inform a clearly defined epidemiological research question, this framework may help identify important addressable risk factors without obscuring ongoing research into causal pathophysiology.

This section introduced the relevance of the DOHaD and the biopsychosocial frameworks to the development of disease across the life course. The next section introduces the mental disorders and behaviour problems under study in the current work, before exploring the existing evidence for life course risk factors of psychopathology.

Measuring psychopathology in epidemiology

Introduction

The current work focuses primarily on affective, anxiety and psychotic disorders meeting the criteria of the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV) (46). The DSM-IV disorders used in the current work include; Post-Traumatic Stress Disorders (PTSD) Generalized Anxiety Disorders (GAD), social phobias, specific phobias, Panic Disorders (PD), Major Depressive Disorders (MDD) and Schizophrenia and related disorders. The DSM-IV is a classification system designed to describe the complete range of mental disorders. Such categorisation allows practitioners and researchers to communicate about mental disorders more effectively, and also provides labels with considerable predictive power for clinical treatment (46). The DSM-IV-TR is a ‘text revision’ of the DSM-IV, with the majority of the changes being only to the descriptive text (47). Appendix 1 (table 1) presents brief definitions of the psychiatric disorders according to the DSM-IV-TR (46).

Anxious, affective and psychotic disorders

The 1997 and 2007 Australian National Surveys of Mental Health and Wellbeing measured the prevalence of adult affective and anxiety disorders, as well as the service usage rates among those meeting the criteria for one or more of the disorders (1, 2) [appendix 1 (Tables 2) compares the 2007 findings of ICD-10 12 month affective and anxiety disorders, broken down by disorder type and gender, with the findings of the 1997 survey (1, 2)]. The 12-month prevalence of any affective disorders remained relatively stable between 1997 and 2007, with the slight increase in 2007 attributed mostly to the inclusion of bipolar affective disorders. Regarding anxiety, it is likely that part of the increase in the 12-month prevalence of any anxiety disorder over the ten year period is due to the use of different versions of the CIDI in the two surveys (48), meaning the criteria of the ICD-10 was operationalised differently (48). National trends of psychotic disorders such as schizophrenia have been examined in the Australian National Survey of Psychotic Illness which has been undertaken twice, once in 1997-1998 and again in 2009-2010 (49, 50). These surveys found that among a sample of public specialized mental health service users, the profile of psychotic disorders had changed little over time with schizophrenia the most common diagnosis among those with psychotic disorders.

Despite the difficulties in establishing trends between the National Surveys, the figures clearly indicate that affective and anxiety disorders are of high prevalence and under treated, and while psychotic disorders have a lower prevalence, the seriousness and persistence of the symptoms results in great social cost. Among the common psychiatric disorders PTSD had by far the highest prevalence in 2007 (see table 2 appendix 1). Beginning with PTSD, the remainder of this chapter describes in further detail the psychiatric disorders and behavioral

problems central to the current work, before exploring the evidence concerning the role of a number of early life course risk factors in predicting these psychopathological outcomes.

Post-traumatic Stress Disorders

It is necessary to briefly describe the history of the current conceptualisation of PTSD, to highlight the competing interests which have helped shape the disorder (51). The intention of including PTSD into the DSM-III was to assess the consequences of traumatic symptoms and the associated impaired functioning in people exposed to an overwhelming experience outside the 'usual' range of human experiences. Consequently, research focused mainly on individuals exposed to objectively defined traumas such as combat, rape or disasters (52). The major change between this earlier conceptualisation, and that found in the DSM-IV is the addition of more traumatic events, and the adoption of a subjective definition of trauma which relies on the individual's reactivity to the trauma.

At a population level, the adoption of a subjective definition of trauma has not offset the increase in the elevated rates of both trauma exposure and PTSD which resulted from the inclusion of additional traumatic events (52). This change has been criticised not only for inflating the disorder's prevalence, but also for broadening the traumatic situations to such an extent that the grouping of such qualitatively distinct events may make it difficult to identify the psychobiologic mechanisms responsible for symptom expression (51). However from a treatment perspective, this broader definition acknowledges the numerous other traumatic events which drive individuals expressing PTSD symptoms to seek professional help (52), and therefore perhaps gives a truer picture of the PTSD which comes into contact with the health care system. The PTSD identified in clinics is defined by the symptoms that drive the patient to seek help, while the type of trauma and immediate reactivity, which is so important in defining PTSD epidemiologically, may be less relevant to clinical diagnosis (52). Thus we

encounter a trade-off in which the increased difficulty in establishing an genesis and therefore the 'true' nature of the disorder, should one exist, is balanced with an increased acknowledgement of a fuller range of PTSD and the linking of these to risk factors which may form the basis for prevention, intervention or treatment for a broader range of individuals.

Some researchers have also felt it necessary to broaden the definition of PTSD. 'Partial PTSD' is considered by some a subthreshold form of PTSD and worthy of study in consequence of the overly stringent DSM-IV PTSD diagnosis (53-55). In addition, 'partial remission of PTSD' originates from findings that many individuals with PTSD will never fully remit and some who do will once again succumb to the disorder in later life (56, 57). Other research groups have made attempts to establish statistical models of PTSD which better reflect the symptom patterns found in epidemiological samples (16, 58). The authors of one such study conclude that the alternative models of PTSD, exhibit a wider degree of heterogeneity and suggest that these alternative models may not require individuals to have symptoms from each category, but instead classify people by PTSD subtype (58). Contrary to these findings, another method, that of taxometric analysis has found PTSD better explained as a dimensional disorder which does not differ qualitatively at levels of severity, but only quantitatively, suggesting that PTSD is simply the extreme end of a normal stress reaction (59, 60). This latter interpretation has been persuasively countered on theoretical grounds (61), but appears empirically meritorious.

Before concluding we must briefly outline the numerous revisions made to PTSD in the DSM-5 which included: (i) the elimination of criterion A2 (the requirement that the traumatic event must elicit fear, helplessness or horror); (ii) splitting the previous three symptom clusters into four, with the additional cluster representing 'persistent avoidance of stimuli

associated with the traumatic event(s)'; (iii) the addition of new symptoms and the revision of some existing symptoms; (iv) the inclusion of a dissociative subtype; (v) the removal of PTSD from the anxiety disorders to a new category of traumatic and stressor-related disorders; and (vi) changes to the definitions of traumatic events (10).

It has been argued that while the prevalence of PTSD is unlikely to change under the new definition, the increased heterogeneity of what constitutes a traumatic event and the introduction of several symptoms occurring in other disorders means the heterogeneity of people receiving a PTSD diagnosis is likely to increase along with the comorbidity with related disorders (7). Comorbidity is a central characteristic of psychiatric diagnoses, partly due to the way psychiatric disorders are conceptualised and categorised in the DSM and ICD systems (62). Perhaps the most common comorbidity between any two DSM-IV disorders is that between major depression and generalised anxiety disorders.

Comorbid Major Depression and Generalised Anxiety Disorders

Unlike PTSD, the central characteristics of the current conceptualizations of the affective and anxiety disorders have been acknowledged and subject to scientific, philosophical and even spiritual enquiry for centuries (8, 13). While the depressive and anxiety disorders described in table 1 are considered to be distinct and separate disorders, the high comorbidity among the depressive and anxiety disorders has led many to question what these comorbid relationships represent (62). In particular, the strong relationship between Major Depressive Disorder (MDD) and Generalised Anxiety Disorder (GAD) has prompted calls for the reclassification of both disorders under the same diagnostic category (63). Such arguments gain additional support due to GAD's historically poor nosological integrity (63). However, over recent revisions of the DSM, GAD has developed relatively rapidly, from a residual diagnosis in DSM-III to a reliable diagnosis characterized by worry, (apprehensive expectation of future

events), in DSM-IV (64). Despite increased specificity, GAD continues to exhibit substantial comorbidity with MDD, and research into how the disorders should be diagnostically related is ongoing.

Some evidence also suggests that both disorders represent different manifestations of a single underlying construct (63). MDD and GAD exhibit higher comorbidity than do other anxiety disorders with MDD (62), with a temporal sequence suggesting that GAD symptoms represent a prodrome of MDD (65). Structural equation models (SEM) show that both disorders load onto the same higher order 'distress disorders' factor (62, 66-68), and twin studies consistently suggest that both disorders share a strongly related genetic substrate (69, 70). On the other hand, longitudinal studies detail a pattern of occurrence and co-occurrence of GAD and MDD too complex to reflect a single underlying disorder (71). Both disorders have been found to occur independently at a substantial prevalence (72) and have unique longitudinal symptom trajectories (73). MDD precedes GAD as often as GAD precedes MDD (74) and baseline MDD is strongly predictive of subsequent GAD (71), reducing confidence in the prodromal explanation and revealing the importance of specifying co-occurrence by the primary disorder. Lastly, longitudinal SEM studies find superior fit when the variance of anxiety and depression is accounted for by a general internalising component with additional disorder-specific components (75, 76).

Recent prospective studies suggest that anxiety and depression are predicted by unique risk factors (71, 73, 77-80). Regarding comorbidity, some of these studies suggest that co-occurrence is more closely related to anxiety than depression, as anxiety and co-occurrence are predicted by the same risk factors, while depression is predicted by unique risk factors (78, 79). Further, primary anxiety remained predictive of later MDD after adjustment for common risk factors, while the reverse relationship was not found (80), suggesting anxiety is

causally related to subsequent MDD development. However, there is also evidence that GAD+MDD is predicted by risk factors unrelated to either GAD or MDD (77), and that GAD+MDD when specified by the primary disorder is not associated with risk factors which differentially predict GAD and MDD (71). These studies have some important limitations, as half used descriptive analyses only, some did not use DSM-IV diagnoses and some were retrospective. Thus, further longitudinal risk factor studies into MDD+GAD are needed with the potential to elucidate novel factors which increase the risk of this serous comorbid condition compared with either discrete disorder, and in doing so reveal if the discrete disorders and their comorbid form have shared or different etiological factors, further alluding to the separability of GAD and MDD diagnoses.

In addition to common mental disorders, enquiry into the causes of rarer and more severe mental disorders remains a critical area of research. The next section describes how recent thinking with regards to conceptualising psychotic disorders affected the way such disorders were represented in the current work.

Psychotic Disorders

Schizophrenia has been recognized as a distinct mental disorder for over a century, but the clinical nature, pathophysiology and etiology remain elusive (11). Generally, delusions and hallucinations are the predominate characteristics of acute clinical presentations, while gradually increasing negative symptoms mark the chronic profile, which are also the major causes of disability and impairment (81). Importantly, the types, combinations and severity of positive, negative, disorganized, cognitive, psychomotor and mood symptoms vary widely among individuals and across the course of the disorder in the same individual. This heterogeneity, which makes determining a precise definition of schizophrenia difficult, also impedes research into etiology (11).

The neurodevelopmental model of schizophrenia offers a solution to the dilemma encountered when attempting to define and dichotomise schizophrenia from normality, and provides a framework for investigating etiological factors. It contends that schizophrenia is the severe and disabling end point of a continuous distribution of psychotic experiences present in the general population (82, 83) and that a number of environmental and genetic factors, either via accumulation or through more complex interaction, are responsible for an individual's movement along this continuum towards a schizophrenia diagnosis (84, 85).

While recent evidence of a dimensional rather than categorical structure of psychosis (83, 86) supports an idea long recognised in psychiatry (82), the impact subthreshold psychotic experiences have upon individuals comprises a more recent line of investigation. Although some reviews suggest the majority of subthreshold psychotic experiences may be transient (85), and be part of the everyday experience for some people (82), contrary evidence suggests that subthreshold psychotic symptoms are a strong predictor of non-psychotic psychiatric disorders (87), predictive of later psychotic disorders in a dose-response manner (85), at higher levels necessitate clinical care regardless of the progression to frank psychotic disorder (88), and are influenced by similar risk factors which predict schizophrenia (82, 85, 89, 90). Thus research into the early life factors thought to predict schizophrenia and related disorders may benefit from attempting to specify the outcome by the underlying symptoms dimensions (91, 92).

The cognitive, motor and behavioural abnormalities found to precede schizophrenia (93-96) are also consistent with the neurodevelopmental model, which sees schizophrenia as the outcome of a process of abnormal neurodevelopment beginning in early life (84). However, studies have so far produced a mixed picture of what these premorbid abnormalities represent. Some evidence supports the notion that they signify the inevitable premorbid

manifestation of a genetic predisposition to later schizophrenia, (93, 97), while alternate evidence suggests that they are influenced by the same early environmental risk factors which influence later schizophrenia (98, 99). This issue will be expanded in relation to studies undertaken in the current work below.

Before concluding, three limitations are noted, with one or more having been found to affect all existing longitudinal studies testing the impact of early life environmental risk factors on later psychotic experiences. Firstly, the importance of subthreshold expressions of psychosis has been underestimated in epidemiological research which relies overly on either structured interview or self-report measures, which do not probe positive responses for truly psychotic content and thereby may overestimate the prevalence of psychotic experiences (100). Secondly, the operationalisation of subthreshold psychosis as either predictor or outcome is often based on a simple experiences count (85), likely ignoring the complicated structure of the psychosis continuum (91). Thirdly, studies testing the impact of early life risk factors on outcomes of psychotic experiences in childhood (101, 102) need to be substantiated by similar studies in adults. This is because psychotic experiences in childhood are more transient and less clinically significant than in later adolescence, as found in one study where the prevalence of subthreshold psychotic symptoms in the community declined after early adolescence but their association with non-psychotic psychiatric disorders increased (87). The current work partly addresses these limitations and investigates the development of psychotic experiences instead of diagnostic categories of psychotic illness.

This section outlined some major issues associated with the main psychiatric outcomes under study in the current work. The remainder of the literature review now considers a number of important and related early life course risk factors which lead to the development of these psychiatric outcomes and the frameworks in which they can be understood.

Prenatal risk factors for later psychopathology

Fetal development and adult offspring psychiatric disorders

Though still contentious, a growing body of evidence across a number of scientific disciplines suggests that sub-optimal fetal growth negatively impacts upon offspring neurodevelopmental outcomes, in addition to physiological disorders. Epidemiological studies testing the association between various measures of birth weight with later psychopathology have found associations with symptoms of distress (103-105), depression (106-111) and/or anxiety (112, 113), stress susceptibility (114), depressive and anxious symptoms (115-118) and psychiatric morbidity (119), which in some cases were found in females only (108, 110, 116, 117). A number of studies which used alternative birth dimensions found associations between higher ponderal index and lifetime depression in women (109), smaller birth length adjusted for gestational length (GA) and child behavioural problems (120), and shorter GA and depression (105). Conversely, a number of well-designed studies have found no association between birth weight with depression and behaviour problems (120-123).

Notably, nearly all the studies found only low to moderate effect sizes, and many studies which found associations on one measure of psychopathology found no association with other measures. A recent meta-analysis concluded that this propensity to emphasise significant findings within papers was evidence for publication bias, which, once adjusted for, reduced the weak aggregate association between birth weight with depression and psychological distress to non-significance (124). Before ruling the relationship non-existent it is necessary to consider the considerable heterogeneity exhibited by the studies: including the study designs, measurement of the outcome and predictor variables, the sample sizes, the participation rates, the effect sizes, adjustment for confounders and the age of participants when the outcome

variables were ascertained. This section explores some of the heterogeneity among the studies, the potential impact of this on the results, and how this can inform future research.

Adjusting for gestational age

Adjustment for gestational age (GA) is fundamental to properly specifying the predictor variable in studies assessing the role of birth weight. Although the aforementioned meta-analysis did not find significant differences in the effect sizes of studies which adjusted for GA compared with those which did not (124), several studies highlight the importance of this factor (104, 107). One study found that a relationship between birth weight and depression in women became stronger once those less than 37 weeks of gestation were excluded from the study (107). Two further studies confirmed that this finding has relevance among those born with very low birth weight (VLBW (111, 119). Adjusting for GA also has strong theoretical importance, as it is believed that different mechanisms account for the causes of low birth weight in those born pre-term and those born full-term, with the latter resulting from intrauterine growth restriction (IUGR) and the former resulting from different pathophysiologies or genetic factors (104). The exact biological mechanisms underlying the association between an IUGR birth phenotype and adult mental health disorder remain elusive, with this birth phenotype seen as a marker that either adaptive or impaired development has occurred during fetal growth (125).

Proposed mechanisms for the relationship

The most salient biological mechanism proposed to explain the association between birth weight and later psychopathology involves alterations to the fetal hypothalamic-pituitary-adrenal (HPA) axis, triggered by stimuli during susceptible periods of gestation, which may influence the secretion of offspring stress hormones in later life (107, 114). Experiments in rodents suggest that maternal nutrient restriction during a critical period of fetal brain

development reduces birth weight and alters offspring behaviour and HPA axis functioning, indicated by altered basal cortisol levels (17, 126), and that maternal cortisol reaches the fetus and is responsible for altering fetal HPA activity (127). This finding is interesting as the fetus is protected from maternal glucocorticoid (GC) by feto-placental 11β-HSD2, which catalyzes the rapid metabolism of cortisol and corticosterone (rat GC) (17). Findings which show that 11β-HSD2 is selectively down-regulated by maternal dietary constraint suggests that HPA programming due to environmental stimuli may be mediated via 11β-HSD2 levels (128). Recent evidence identifies epigenetic remodelling of chromatin in response to prenatal insults as responsible for permanently altering the HPA axis and stress response in offspring by altering the expression of the genes for the glucocorticoid receptors and 11β-HSD2 (129).

While experiments on humans are not possible, observations have found increased levels of fetal cortisol in growth restricted human fetuses (130). Adults born with low birth weight had increased salivary cortisol response to laboratory stress tests when compared with normal birth weight controls (131). In humans, placental insufficiency rather than nutrient restriction would be the likely cause of IUGR in Western nations, occurring when the placenta fails to supply adequate nutrients and oxygen to the fetus (104), and animal studies have confirmed that placental insufficiency is associated with increased levels of GCs *in utero* (132). From a programming perspective, increased GCs may signal an adverse uterine environment, thereby mediating the effects of maternal undernutrition or placental insufficiency in an attempt to adapt fetal development to maximise survival likelihood (17). The current work does not have the capacity to extend biological and epigenetic understandings of the association between birth weight and later psychopathology, and it was discussed here to illustrate what may underlie the epidemiological associations.

Non-linear associations in epidemiological studies

Another important finding comes from epidemiological studies showing a significant non-linear association between birth weight and psychopathology. In one study in which birth weight was divided into groups by deciles, the mean score for the stress test improved with increasing birth weight until 4200g, after which it began to worsen (114). In another study, birth weight z-scores were divided into groups by quintiles and it was found that those in the lowest and highest quintile groups were at higher risk of anxious and depressive symptoms (115). Lastly, one study found high birth weight (>3.5 kg) was protective of GAD diagnosis, but no difference in risk between normal and low birth weight (<2.5 kg) (113). Conversely, three studies which divided birth weight into three, four or seven categories (107, 112, 133) found linear trends with better outcomes at higher weights. While these findings may at first appear contradictory, the largest category for birth weight among the studies finding linear (i.e., protective effects of higher birth weight) was >3,500g in three, and only >4,000g in the fourth (133). Given that the average birth weight in Australia in 2004 was 3,370g (134), these studies likely did not have a category high enough above the mean to test for adverse outcomes among the heaviest babies and evidence that over-nutrition during pregnancy is associated with poor offspring outcomes suggests that testing for non-linear relationships across the full range of birth weights may prove useful (135).

Specification of the psychiatric outcome

While the studies vary considerably in methodological approaches, much of the inconsistency in the findings may be traced to two issues related to the outcome variable. The first relates to greater specification of the psychopathological outcome by the use of specific clinical diagnoses drawn from a semi-structured interview, rather than broad-band self-report symptoms of psychological or behaviour problems. Although it has largely been believed that birth weight is a risk for generalised psychopathology (113), it may not be so, and the use of

specific diagnoses may lead to replicable findings by identifying aspects of psychopathology related to fetal development (e.g., phobic symptoms compared with worry). The second seemingly paradoxical issue is that some of the specific disorders have such high levels of comorbidity (i.e., MDD and GAD) that it should be explored to reduce the potential that results are confounded by the outcome (i.e., anxiety by depression, or vice-versa). While roughly half of the studies have used clinical diagnoses, only a few of these used specific diagnoses including MDD (112, 122), GAD (113) and depressive disorder (106, 110).

Potential confounding factors

Evidence from epidemiological and biological studies suggests a number of factors may confound the relationship between birth weight and later psychopathology, and which should therefore be accounted for in a properly specified model. Gender is important, as females on average have lower birth weight, and are more likely to experience a common mental disorder (1). Less obvious is gender's interactive role, by which the effect of birth weight on an outcome is suggested to be different in females and males. Although a number of studies claimed to have found sex-specific results (108-110, 113, 116, 117), without formally testing for an interaction a conclusion of a sex-specific effect should not be drawn. Of the studies which demonstrated a significant sex interaction one found the risk was increased for males (113), while the other found the reverse (108), and a third study with a small sample size (n =244) and therefore limited statistical power, found no gender differences (112). Interactions between adverse maternal or placental conditions with gender do have a biological basis. Firstly, because the male and female fetus have different growth trajectories which would make males and females susceptible to stimuli at different periods (115), and secondly, because evidence shows that GCs transfer in larger concentrations across the placenta of the female fetus, compared to the male fetus (17).

Birth weight may partly reflect lower socioeconomic status (SES), with this disadvantage also leading to higher rates of mental illness (133). One study found that adjusting for SES noticeably reduced the association between birth weight z-score and the depression/anxiety subscale (115). However, all but two studies reviewed here (110, 114) adjusted for a measure of SES, and aside from that mentioned above, none reported that such adjustment was important to the primary relationship. This lack of associations may be due to these studies having limited capacity to measure the social gradient effect in a satisfactory manner (115).

Maternal smoking, particularly during the second half of gestation, is also associated with SGA births (136) and IUGR (17). Smoking during pregnancy has been found to be associated with increased risk of ADHD symptoms in children, independent of antenatal stress (137) and SES (138). In adolescents, smoking in pregnancy has been associated with an increased risk of depression (139), and aggressive and externalizing behaviour problems (140). Prenatal smoking may cause IUGR due to the stimulation and secretion of vasoconstrictive catecholamines by nicotine or from restricting fetal access to oxygen by the intake of carbon monoxide (136). More recently however, studies using assisted reproductive technologies suggest that either genetic or environmental factors related to smoking are responsible for the association and not smoking itself (141). Despite this uncertainty, prenatal smoking represents a key cofounding variable, and while the majority of studies adjusted for maternal smoking (103, 106-109, 111, 112, 115, 120, 133), some studies took retrospective measurements of cigarette consumption during pregnancy (106, 107, 112, 133).

While moderate and low levels of maternal alcohol consumption during pregnancy have not been associated with IUGR, there is evidence linking such levels with reduced writing and arithmetic ability in children and negative impacts on brain development in animal models (136). Due to this and the rare but destructive consequences resulting from high alcohol intake

during pregnancy (136), alcohol should be considered as a potential confounder despite being ignored by all but a few studies (108, 112, 115). Many studies controlled for maternal age at birth (104, 106-109, 111-113, 120, 122, 123, 133), as both teenagers and older women are at an increased risk of delivering a low birth weight baby, along with an increased risk of a number of other adverse obstetric outcomes. It is understood that these increased risks are associated with the lower socio-economic backgrounds of teenage mothers, and with the biological processes of ageing in older mothers (142). Some studies also adjusted for maternal parity (103, 104, 107, 112, 115, 120), as it has been shown that increasing birth order is linearly associated with a birth weight increase in full term offspring (143).

Fianlly, the effect of maternal psychopathology during pregnancy may account for the association between smaller birth phenotype and offspring mental disorders, as subjective measures of antenatal anxiety or stress are associated with lower birth weight and pre-term births in humans (144-146). The mechanism by which antenatal maternal anxiety leads to smaller birth weight and shorter gestation also involves HPA programming. Despite this, less than half of the studies reviewed here adjusted for a measure of maternal mental disorder, and some of these included only a history of mental illness rather than prenatal exposure (108, 109, 112, 113, 115, 122, 133). Maternal prenatal anxiety has also been found to be independently associated with offspring mental illness, with a persistent but reduced effect after adjustment for birth weight, GA and concurrent maternal psychiatric measures (147, 148). Thus in addition to being an important confounder, prenatal psychopathology also potentially predicts later offspring psychopathology and is described in detail in the following section.

Non-genomic transmission of psychopathology from mother to child

While psychopathology is known to have a heritable component, growing evidence suggests that exposure to subjectively assessed maternal psychopathology including depression, anxiety and stress during pregnancy, may permanently alter the development of key regulatory systems of the fetus, which may in turn increase the risk of psychopathology in the offspring. A number of epidemiological studies support the hypothesis that prenatal psychopathology impacts later offspring psychopathology via a biological mechanism occurring *in utero*, but that the effect is partly confounded and/or modified by additional prenatal and postnatal environmental factors and (epi)genetic factors (149). Though the studies are of a high quality and supported by biological evidence, replications in cohorts at later developmental stages are scarce.

Previous epidemiological findings

Existing studies can be broken up into three main themes or aims. The first group, largely comprising the earliest studies, demonstrated that associations remain even after adjustment for potential confounding factors. In these studies maternal prenatal anxiety predicted offspring behavioural and emotional problems at age 47 months (150); inattentive/hyperactivity and emotional problems, and conduct disorders at age four years (151); and symptoms of ADHD, externalising problems and anxiety at age 8-9 years (147). One study found that the relationship between maternal prenatal depression and adolescent offspring depression was mediated via ongoing depression in the mothers (152). A later study also found that prenatal maternal anxiety predicted internalising but not externalising disorders, and prenatal and post-natal maternal depression predicted both outcomes at age 7-8 years (153). In these studies associations remained after adjustment for maternal postnatal

psychopathology, SES, obstetric factors (including birth weight and gestational age), and prenatal smoking and alcohol use.

The second group of studies used innovative designs with the purpose of testing if the association could be better explained by residual environmental or genetic factors. One study found that both paternal and maternal anxiety and depression during pregnancy were risk factors of equal measure for child attention problems at age 4 (154). Another study found that increased prenatal maternal anxiety did not impact on adolescent cognitive ability, depression or conduct disorders after adjusting for these same outcomes in the mothers (155). However, a later study by the same team of investigators found prenatal maternal depression remained predictive of adolescent antisocial behaviour after adjusting for maternal (though not paternal) history of conduct disorders (156). A recent study used a 'prenatal cross-fostering' design to assess the risk of prenatal stress on offspring ADHD between women whose IVF pregnancy was related or unrelated to them genetically, finding the association was only present in genetically related dyads and therefore likely to have a genetic origin (157).

The third group includes two of the most recent studies which explored factors potentially modifying this relationship. The first study found that the main effects of prenatal maternal depression and childhood maltreatment at age 11 did not predict depression and conduct disorders at age 11 and 16, but children exposed to both factors had almost 12 times the risk of both outcomes (152). The second study did not identify a relationship between prenatal maternal depression and offspring psychopathology but used a mixture modelling approach to determine how maternal life course trajectories, during and after pregnancy, moderated the impact of contextual risks and dependent interpersonal stress on later child psychopathology (158). This study informed the methodological approach of the current work by specifying maternal psychopathology using empirical longitudinal trajectories.

Gaps in the epidemiological literature

Epidemiological studies assessing the risk of prenatal psychopathology have been methodologically superior in many ways to those assessing the risk of birth weight. Not only do the former account for an impressive range of prospectively ascertained measures and confounding variables, but more recent studies have been innovative in both study design and statistical modelling as described above. However, unlike studies which assessed the impact of objective stress during pregnancy (detailed in the next section), the impact of subjective maternal mental health and stress has mostly been assessed for its impact on children and adolescents. Of the studies described above, only four included outcomes during adolescence (152, 155, 156, 159), while none assessed outcomes during early adulthood. Some of the only studies to have assessed the outcome during adolescence are derived from the same small sample ($n \approx 120$), with limited capacity to identify which time-point is most significant to offspring outcomes.

Measuring maternal prenatal distress

Another methodological consideration relates to how maternal psychopathology has been conceptualised and measured. The majority of studies assessing the role of prenatal or postnatal mental health have focused on maternal depression, with anxiety sometimes and subjective stress often not accounted for or discussed (141, 160, 161). The strong correlations among symptoms of depression, anxiety and stress observed during pregnancy and in the early post-natal period suggest that the three constructs are difficult to distinguish empirically, and studies may benefit from instead focusing on a single domain of 'distress' encompassing symptoms of depression, anxiety and stress (160-162). By ignoring this empirical and theoretical overlap, focusing on a single psychological construct serves to overemphasise whichever construct is tested in isolation (160). Furthermore, while testing the

separate effect of all three constructs may serve to identify the strongest predictor, it overlooks the increasingly severe symptoms known to occur in those with psychological disturbance across multiple constructs (160, 161). It may also lead to weaker associations as the predictive power of the three constructs are artificially separated.

A related limitation is the difficulty in assessing infant and childhood psychopathology, which has mostly been assessed by the offspring's mother and therefore may be biased by her own experience of mental health problems (141). This is supported in one review, which concluded that the impact of prenatal psychopathology was stronger on both offspring internalising and externalising problems when offspring behaviour was assessed by mothers instead of teachers, clinicians or the offspring themselves (163). Thus, future studies may expect to identify more robust associations if able to ascertain measurements of offspring psychopathology from the offspring themselves.

Proposed mechanisms of the relationship

Looking briefly at the proposed biological basis of the relationship, experimental evidence from studies in non-human primates and rodents suggest that antenatal stress leads to HPA dysregulation in offspring, with both species showing higher basal GC levels as a result of antenatal stress (164, 165). Further findings show that the offspring of rats who were stressed during gestation, exhibit enhanced anxious behaviour (17), while more recent findings suggest that increases in maternal corticosterone may be sufficient to increasing anxiety related behaviours in offspring (166), which is also linked to structural and functional changes in the offspring brain (167).

Biological studies in humans appear to corroborate evidence from animal experiments, finding that even after adjustment for obstetric, sociodemographic and concurrent maternal depression and anxiety, differences in offspring awakening cortisol were associated with

prenatal anxiety (168), and that prenatal anxiety increased depressive symptoms in adolescent female offspring, which was accompanied by a high, flattened day-time profile of cortisol. (169). A recent study in humans found that the relationships between maternal prenatal depression and anxiety with poorer neurodevelopmental outcomes in infants, were mediated via increased methylation of placental GR and 11β-HSD2 genes respectively (170), suggesting epigenetics may also underlie the permanent alteration of stress hormones. Thus while the evidence for the biological basis of the relationship between prenatal psychopathology and later psychopathology in offspring is strong, further epidemiological research is needed to determine if these relationships translate to meaningful negative developmental outcomes at later ages.

Alternative explanations for the relationship

Research aiming to incorporate the ideas described above must also have the capacity to account for relevant confounding factors including birth weight (adjusted for GA), prenatal smoking and alcohol use, maternal age, parity and SES (149). There are three processes which may additionally explain the relationship between prenatal and offspring psychopathology.

Firstly, mothers experiencing prenatal psychopathology during pregnancy are more likely to experience psychopathology in the months and years following pregnancy (171), and this ongoing exposure may explain the relationship between the prenatal exposure and offspring outcomes. Statistical adjustment for measures of psychopathology postpartum has been found to attenuate but not remove the primary association (150, 151, 172), revealing that the two are related but may have independent effects. Theoretically postnatal maternal psychopathology can impact directly on the offspring via parental modelling of depressive and anxious behaviours, increasing the child's threat perception and learned helplessness (173). It may

also act indirectly by impairing maternal parenting (i.e., increasingly withdrawn and disinterested in quality) (174). During the earliest stages of development, maternal rearing may play a vital compensatory role for the baby's limited ability to regulate negative emotional states, protecting against excessive arousal and fostering emerging abilities of self-regulation (175).

Secondly, shared environmental factors present before and after birth, may be responsible for increasing both mother and child psychopathology (158). Such factors will include not only contextual factors such as SES, but also what Hammen termed dependent interpersonal stress (DIS) factors, which includes maternal relationship quality and exposure to stressful life events (176). The difference being that the contextual risks are considered to have an independent impact on psychopathology, while the DIS factors and psychopathology may have a bidirectional relationship (i.e., relationship problems can increase depression, while depression can also cause relationship problems) (158, 177).

Thirdly, the role of genetic continuity in the proposed relationship, that the mother's distress represents a genetic predisposition to psychopathology with manifestations of psychopathology in the offspring simply heritable, is not easily accounted for in most available population-based birth cohorts. Most epidemiological studies have accounted for genetic continuity, by adjusting for either a history of, or for ongoing maternal distress after pregnancy, as proxy indicators of genetic continuity (149). Further, most existing research has not considered the role of the father's mental health, thereby ignoring the father's contribution to offspring mental health via parenting or genetic inheritance (154).

In summary, the current work aims to contribute to the literature reviewed here by testing the relationship among older offspring, and by applying a sophisticated statistical model in an effort to better account for and identify the periods (i.e., prenatal or postnatal) when

subjectively assessed maternal depressive, anxious and stress symptoms have the greatest impact on offspring development (see the methodology). The next section introduces measures of maternal psychological and physical health during pregnancy which are more objective and believed to impact on later offspring psychotic experiences.

Prenatal risks and early postnatal mediators of psychopathology

Maternal prenatal stressful life events and offspring psychotic experiences

When conceptualising and measuring maternal prenatal 'distress', the literature is broadly divided into objective (independent stressful events) and subjective (psychopathology) (141, 178). Studies which have used objective assessments of prenatal stress have usually ascertained the degree of exposure of the pregnant mothers to a natural or man-made disaster. Prenatal exposure to earthquake, flood, famine, military invasion, and death of a close relative increase the risk for adult offspring affective, psychotic and autism disorders (179-185). Further studies have found that prenatal exposure to disasters (186, 187) and severe stressful life events (188) predicted HPA abnormalities among offspring. While these studies have shown that prenatal exposure to stressful events represents a non-specific risk factor for a number of adult psychiatric disorders and other outcomes (189-191), a number of studies have found significant associations with psychotic illness (179, 183, 184, 192). These findings are further supported by studies in rodents showing that prenatal stress predicted a number of morphological and neurochemical brain alterations associated with schizophrenia in the offspring (193).

Assessing the impact of objective stress rather than subjective psychopathology on offspring psychopathology has several methodological advantages as it is likely to reduce or eliminate; (i) the bias which stems from mothers assessing both their own mental health status and that

of their offspring, and (ii) confounding by genetic continuity, as maternal exposure to the event will not be determined by genetic factors (178). Despite these advantages, objective exposures to stress may have less public health relevance compared with the much higher prevalence of subjectively assessed psychopathology. One solution to the problem of subjectively versus objectively measured psychopathology is to test the effect of a broader range of 'everyday' cumulative stressful life events on offspring outcomes (e.g., family member has developed a serious illness, difficulty finding accommodation, etc.). This may reduce the bias and confounding associated with subjective assessments as discussed previously while representing events more prevalent than disasters. Though it must be noted that unlike disasters, every day events will to some degree be determined by maternal personality and mental health.

The relationship between prenatal stressful events and psychotic disorders

With regards to the relationship between stressful life events and psychotic disorders, a recent study investigated the impact of stressful life events during pregnancy on the risk of sub-clinical psychotic experiences, rather than disorders, in offspring aged 12 years (102). This was the first study to test the relationship between prenatal stressful life events and increased risk for subclinical psychotic experiences, and suggested that exposure to prenatal stressful life events may have relevance to the neurodevelopmental model of psychotic illness (discussed in section 2.1.5). There are however a number of ways future research could extend these initial findings, including the investigation of offspring psychotic experiences at later developmental stages when psychotic experiences are known to be more serious (87), in addition to better accounting for the many prenatal and perinatal factors which are also predictive of later psychosis (92).

Incorporating premorbid abnormalities into the causal pathway

A major innovation to future epidemiological studies testing the association between prenatal stressful life events with schizophrenia and psychotic illness would be to incorporate the premorbid cognitive, motor and behavioural abnormalities noted to precede a schizophrenia diagnosis in the earlier years of development (93-96) into a 'causal' pathways model. There are currently inconsistent findings with regard to what these premorbid developmental abnormalities represent, and incorporating them into such a model might shed some light on their role in the neurodevelopment of schizophrenia. They may be the inevitable premorbid manifestation of a genetic predisposition to schizophrenia, or they may result from the same environmental risk factors which predict schizophrenia. One study concluded that as unaffected siblings showed similar elevations in premorbid abnormalities to siblings with schizophrenia compared with controls, the abnormalities were likely to reflect a genetic predisposition, rather than the contribution of shared environmental factors (93). Another study also supports the idea that the premorbid developmental abnormalities may be of a genetic origin, as obstetric factors could not entirely account for the developmental abnormalities which preceded schizophreniform disorder (97).

More convincing evidence found that while obstetric complications did not predict later schizophrenia, those with obstetric complication and delayed motor development had an increased risk of schizophrenia (194). This may be explained as a gene × environment interaction, such that obstetric complications (environment) moderates the level of expression of a gene associated with increased schizophrenia risk, and developmental delays indicate the presence of the gene (195). However, two studies using another prenatal complication, namely maternal infection, predicted both premorbid developmental abnormalities and later schizophrenia (98, 99). One of the studies suggested that a brain lesion induced by prenatal exposure to rubella led to abnormal neurodevelopment (i.e., cognitive declines) in childhood and schizophrenia after adolescence (98). Here the environmental exposure increases the risk

of schizophrenia and is mediated via premorbid developmental abnormalities. The second study supported a similar mediation effect, but also suggested that additional unknown genetic and/or environmental factors are necessary to make the prenatal brain susceptible to the increased premorbid cognitive abnormalities and psychotic disorders caused by prenatal influenza, as influenza did not influence cognitive ability in control subjects (99). Considering the equivocal evidence, which is based on a number of different early life environmental exposures, studies attempting to incorporate indices of premorbid developmental abnormalities into the causal pathway should assess epidemiologically whether the risk of the environmental factor on later schizophrenia is mediated or moderated via the premorbid abnormalities. Such an approach has great relevance to the neurodevelopmental model of schizophrenia (see paper six).

The next section considers the potential role of another prenatal exposure, infection, which although long implicated in the risk of psychotic (and non-psychotic) mental illness, has recently inspired renewed and more rigorous research interest paralleling the increasing recognition of the neurodevelopmental model of schizophrenia.

Maternal prenatal infection

In addition to indicators of fetal development, maternal mood disorders and stress, indicators of maternal physical health during pregnancy, including gestational diabetes, pre-eclampsia, obesity and birthing method, have been found to have an impact on offspring development (196). With regard to psychotic illness, one line of research has focused on the increased risk of schizophrenia among offspring exposed to prenatal maternal infection (197). Since the first evidence of this association (198), epidemiological studies have moved from relying on ecological exposures, such as comparing the rates of schizophrenia among adult offspring whose mothers were pregnant during an influenza epidemic to later cohorts who were

unexposed, to using exposures at the individual level and specific to the type of infection (197). A recent meta-analysis included a number of population-based studies testing the effect of a range of specific infections determined by clinical diagnoses and serological assays (199). The findings for most types of infections studied were mixed, though of the infections which may lead to an increased risk, three are highly prevalent in pregnant women and include influenza, toxoplasma gondii (T. gondii) and genital/reproductive infections, potentially accounting for 14%, 13% and 6% of total schizophrenia cases (197). Thus, if future studies were to provide clearer evidence that these infections during pregnancy increased schizophrenia risk, then ideally a third of cases could be prevented.

Proposed mechanisms for the relationship

There are a number of possible biological mechanisms thought to underlie the association between prenatal infection and schizophrenia. One of these is familiar, involving the inhibitory effect of prenatal infection on placental 11β-HSD2, which in turn allows increased stress hormones to cross the placenta, permanently altering offspring HPA activity and increasing the risk for schizophrenia in later life (199). Alternatively, some maternal infections may be transmitted to the fetus during gestation via the placenta and directly impact on fetal neurodevelopment (200). Evidence from rodent models shows that infection with human influenza during pregnancy leads to a number of structural and functional changes in the offspring brain associated with schizophrenia, along with behavioural and pharmacological changes in adulthood also associated with schizophrenia (193). More recently, experiments on non-human primates have shown that prenatal influenza infection leads to long-term brain abnormalities (201). Others have reasoned that the action of pro-inflammatory cytokines may be responsible for the increased risk of schizophrenia, and represent a common immune system pathway via which a variety of infections are found to

impact schizophrenia risk (199). This hypothesis is supported by experiments showing that prenatal administration of particular exogenous pro-inflammatory cytokines results in the same schizophrenia-related outcomes among offspring as prenatal influenza infection (193).

The case for mediation and moderation

The high prevalence of exposures such as prenatal stress and infection and the low prevalence of schizophrenia and related psychotic disorders indicate that further factors must be involved in determining whether or not these exposures result in schizophrenia (201). While genetic factors are likely involved, the discord between the prevalent exposure and rare outcome could also be explained by the "two hits" hypothesis, by which prenatal infection interacts with a later postnatal environmental exposure like trauma or substance abuse to result in schizophrenia (202). Another study surmised that prenatal maternal immune activation may act as a 'disease primer' leaving individuals vulnerable to schizophrenia should they be exposed to further environmental insults in later life (201).

Considering the emerging emphasis on the interactions among multiple environmental exposures, a noteworthy omission of the epidemiological research into prenatal infection is how this exposure is related to ongoing offspring illness in early postnatal development. A number of studies have found that a range of infections (203-206) during childhood increase the risk of later schizophrenia and other psychotic disorders (203). Originally it was thought that associations were restricted to infections of the Central Nervous System (CNS) due to their direct neurological involvement (203, 206). However, it is now believed that a range of common infections not directly involved in the CNS (207), and even atopic disorders including asthma and eczema (208, 209), may increase schizophrenia risk. Given the range of infections and disorders found to predict later schizophrenia it is likely that a common

mechanism underlies the relationships, with the most likely explanation being the action of pro-inflammatory cytokines on the developing brain (203).

Despite potentially sharing a similar biological mechanism, and the possibility that prenatal infection and early postnatal illness may be related, research has not tested how these two exposures associate to predict schizophrenia and related disorders. There are a number of ways in which the relationship between the two exposures may result in an increased risk of schizophrenia: (i) they may represent independent risk factors, having separate effects on schizophrenia; (ii) the exposures may be confounded by one another, with adjustment revealing the period in which the developing brain is most sensitive to the risk of schizophrenia posed by exposure to illness and infection; (iii) they may combine to have a cumulative effect on schizophrenia, such that exposure to both is necessary to increase schizophrenia risk, or exposure to both leads to an elevated risk of schizophrenia above that contributed by either one exposure alone (i.e., additive or multiplicative interaction); (iv) prenatal infection may indirectly increase schizophrenia risk via early postnatal illness, with mediation perhaps indicating that maternal prenatal infection was transmitted to the fetus (197) and resulted in persistent or recurrent postnatal illness (200) which increases schizophrenia risk (203); (v) other factors may explain the relationship between either exposure with later schizophrenia, such as pre-eclampsia, birth weight, preterm birth, induced labour, and fetal hypoxia (101, 210-213).

Alternative explanations for the relationship

Lastly, we must also consider the relationships between both exposures and schizophrenia may be spurious, due to other unmeasured factors which unlike perinatal abnormalities are not causally related to schizophrenia. A recent study found no significant association between maternal prenatal infection and schizophrenia, but did find both maternal and paternal

infections before and after pregnancy increased the risk of offspring schizophrenia (214). Thus, it may be that a general family liability to infection partly explains the relationship between prenatal infection and schizophrenia, via either familial genetic or lifestyle factors which are themselves related to schizophrenia risk (214). Mental illness is more common among members of families of lower socioeconomic status and with poorer lifestyles, and these same factors may also drive an increase in infection occurrence (199). Alternatively, a shared susceptibility to illness and psychotic illness may have a genetic origin, as evidence links several genes associated with schizophrenia risk to those associated with the major histocompatibility complex on chromosome 6, which is responsible for immune system activity (215). Thus, epidemiological studies which explore how prenatal infection and early postnatal illness associate to predict schizophrenia are warranted. Further, there is a need for such studies to employ more sophisticated statistical models with the ability to properly account for the interactions among multiple exposures, to both confirm and explain the importance of prenatal infection (199).

The final section of this literature review explores additional risk factors during childhood and adolescence with particular relevance to the gender specific risk of post-traumatic stress.

Childhood and adolescent risk factors for psychopathology

Gender differences in coping with traumatic stress following assault

Child and adolescent development also mark periods in which environmental factors may increase the risk for a wide range of non-communicable diseases in later life (37). While some risks during early development may impact on later health in a manner congruent with the DOHaD hypothesis, the gendered response to traumatic exposure in childhood and adolescence likely results from the interaction between biological, psychological and social

influences (216). A good example is the increased risk of PTSD in women (43, 217-220). Originally this increased risk was thought to be due to the higher incidence of sexual violence against women. Evidence suggests however that there is no difference in the conditional probabilities of developing PTSD by gender in consequence of adult or child sexual assault, but that females are more likely to develop PTSD due to other traumas (219). In particular, studies and reviews continue to identify an increased female risk to exposure to non-sexual assault (43, 219-224).

Proposed mechanisms for the relationship

Support for a female vulnerability to stress is also found in animal studies, with females showing increased HPA activity in response to administration of an early life stressor, though similar (but non-experimental) findings in humans are mixed (225). Animal studies have also implicated sex-specific epigenetic changes relevant to learning and memory in response to early life stress, which could be responsible for long-term alterations in HPA activity after exposure to stress (226). Another study in humans found that the increased risk of PTSD in females was explained by pre-existing elevated rates of anxiety and somatoform disorders, which if present before traumatic exposure are thought to increase the risk of developing PTSD (224). However, this finding was not substantiated in a later study, which instead suggested sex-specific stress impacts of depression, anxiety and neuroticism may hold more promise for understanding the female risk (221). Another study concluded the higher rate of PTSD in women was the product of a generally increased vulnerability to emotional stress, demonstrated by female gender no longer predicting PTSD once adjusted for the perceived severity of the trauma (220). Others concluded that female vulnerability to assaultive trauma came due to a higher risk of females experiencing avoidance/numbing symptoms than males post-exposure (223).

The role of poorly specified assault events as part of the gender increase of PTSD

Despite evidence for sex-specific reactions to trauma at the biological and psychological levels, the gender specific response to trauma found in epidemiological studies may be caused by unmeasured aspects of the trauma which differ between males and females. For example, several reviews concluded that female-victim physical assaults are more likely to be perpetrated by an intimate partner, more likely to result in serious injury being committed by a stronger attacker and may involve a real or perceived threat of sexual violence (219, 227). Furthermore, social roles may partly dictate the course of PTSD symptoms following assault, as females may receive lower levels of social support following trauma due to the stigma surrounding intimate partner violence (228). The same could be said for males who experience sexual assault and rape, and studies suggest that males may be at higher risk of PTSD following these traumas, perhaps because male sexual victimisation receives less attention and is an experience which may be damaging to male masculine identity (227). Despite the limitations of survey data, observed sex differences in PTSD require further investigation, and early life factors may help determine how trauma differently relates to PTSD in men and women.

Early childhood cognitive development and traumatic stress

One early life risk factor which may partly explain the increased female-specific risk to PTSD and prove informative to early intervention is pretrauma cognitive ability. Lower levels of early life cognitive ability or intelligence have been found to increase the risk for depression and anxiety, with the association either only found, or found to be stronger in females (229-232). A recent review of the ten prospective studies, which had the capacity to account for a measure of pretrauma psychopathology, found that lower pretrauma cognitive ability increased the risk for PTSD (233). These studies can be divided into

military/emergency services personnel and civilian studies. The first group of studies suggest that various measures of pre-combat/pre-service cognitive ability and IQ predict PTSD risk in returned soldiers and in emergency service personnel (234-238), though one of these studies found that higher cognitive ability was advantageous only to those exposed to lower levels of combat (239).

The second group of studies tested the hypothesis among civilian populations. One used principal components analysis (PCA) to construct a high quality measure of childhood intelligence and found an association between intelligence and PTSD (240). However, during the ascertainment of PTSD, participants who were exposed to trauma but did not experience acute reactivity were coded as not exposed to trauma, thereby likely misclassifying what were potentially the most resilient individuals as unexposed. Further, this study did not specify the trauma type, a factor which is strongly associated with PTSD (14, 241). Another study found no association, a result likely attributable to the indicator variable used which was simply a measure of reading readiness taken at the commencement of schooling and is not considered a reliable measure of intelligence (242).

A third study found a positive association (243), however the sample had a mean age of 17 and was yet to pass through the peak age of trauma exposure. In addition, trauma type was only specified as assaultive and non-assaultive, perhaps oversimplifying the high variability among the different traumas in predicting PTSD in males and females, particularly concerning sexual and non-sexual assault (14, 241). The final study found that lower performance on a number of neurocognitive measures predicted an increased risk in symptoms of re-experiencing and arousal in a community of young adults exposed to a large bushfire (244). Assessment of traumatic stress did however not include avoidance symptoms, and the sample was recruited at age 22 meaning earlier factors important to both cognitive

and psychopathological development were not accounted for. Notably, none of these studies tested for gender effects.

Proposed mechanisms for the relationship

The mechanism underlying the relationship between IQ and PTSD remains unclear. There are two main explanations, each based on limited evidence. The first emphasises a biological process, suggesting that both lower IQ and mental disorders are the result of a general brain vulnerability (235) which may itself result from impaired neural development during fetal growth or early infancy. There is evidence of an association between low birth weight with both lower intelligence and increased risk to anxiety and depressive problems (245). It is also possible that early infant and childhood exposures such as maltreatment, neglect or malnutrition may lead to lower cognitive ability, a greater chance of being exposed to later traumas, and a greater vulnerability to the resulting PTSD symptoms (232, 246, 247). The second explanation emphasises a psychological process and sees intelligence impacting on the individual's capacity to process information associated with the stressful event, increasing the individual's ability to build a narrative and meaning about the trauma they experienced (234, 236, 238, 248).

Importantly, if specific indicators of neurocognitive function (e.g., declarative memory) are found to be involved specifically with PTSD risk rather than general psychiatric morbidity, this would make the general vulnerability hypothesis less likely (249). One study found that unremitting PTSD was linked to a measure of cognitive ability and smaller hippocampal volume, which were also present in non-trauma exposed twins, suggesting these vulnerability factors may have genetic origins and predispose an individual to PTSD (250). Further, the impact that poor coping ability has on the functioning of the individual's stress response may be moderated by gender (229, 232). Lastly, available population studies have failed to

examine how the relationship between cognitive ability and PTSD may be moderated by gender and other factors, possibly due to studies lacking the statistical power to detect interactions.

Aims and objectives of the current work

The final section of this chapter outlines the aims and objectives of the current work, before moving on to describe the methodology. The aim of the present work is to identify risk factors of mental disorders which can be used to inform primary prevention and further research, and by doing so increase confidence in the viability of population preventative approaches to mental disorders. The aims which correspond with the chapters to come and the objectives which correspond with the papers within are explained here in simple and conceptual terms.

- **Aim 1: The impact of restricted fetal growth on offspring mental health**
    - Objective 1(a): Testing the association between lower birth weight and anxiety disorders in young adult offspring.
    - Objective 1(b): Testing the association between lower birth weight and comorbid major depressive and generalised anxiety disorder in adult offspring.
- **Aim 2: The impact of prenatal subjective symptoms of mental health problems on offspring behavior problems**
    - Objective 2(a): Testing the relationship between maternal depressive, anxious and stress symptoms on adolescent offspring behavior problems.
    - Objective 2(b): Testing the relationship between maternal depressive, anxious and stress symptoms on adult offspring behavior problems and depressive symptoms.
- **Aim 3: The impact of perinatal insults on psychotic illness**

- Objective 3(a): Investigating the association between prenatal infection and later psychotic experiences.

- Objective 3(b): Investigating the association between prenatal maternal stressful life events and later psychotic experiences.

- **Aim 4: Sex-specific risks for the development of Post-traumatic stress disorders**

  - Objective 4(a): Testing for a sex-specific effect in the association between childhood cognitive ability and the risk of later PTSD.

  - Objective 4(b): Testing for an increased risk to PTSD following exposure to physical assault in females compared with males.

Chapter 3 - Sample and Methodology

The current work draws on a broad range of data from each completed follow-up of the MUSP to predict which early life course risk factors predict offspring psychopathology at ages 14 and 21. The MUSP, the primary measures and the statistical analyses are described in this chapter, though much information concerning the variables can be found in Appendix 2.

The Mater University Study of Pregnancy (MUSP)

The sample and participants

The MUSP is a prospective pre-birth cohort study which began recruiting pregnant women in January 1981 continuing until 1984 at the Mater Misericordiae Hospital (MMH) in Brisbane, Queensland. Three to five year pregnancy outcomes were the initial focus (251); a wide range of biological, sociological and psychological factors thought to contribute to adverse pregnancy outcomes was collected (252). The study has since continued to follow the mothers and their children, collecting over 2000 items of data across areas including socio-demography, lifestyle, mental health and wellbeing, physical health and anthropometry (251). The last completed data collection of the children was in 2003, referred to as the 21 year follow-up. Approval for each follow-up was obtained from the University of Queensland and Mater Misericordiae Hospital institutional ethics committees. Informed consent was gained from all participants at each stage. All data were coded for confidentiality.

The sampling frame included all pregnant public patients attending consecutive obstetric clinic visits at the MMH. Private patients, patients in need of intensive neonatal care and those transferred to other hospitals were excluded (252). Of 8,556 women who were invited to participate, 8,458 agreed (response rate = 99%), and 7,631 gave birth to a live singleton

baby, of which 7,223 constitute the birth cohort (251) (see figure 1 in appendix 2 for a description of MUSP recruitment and participation across all measurement waves). In this time-frame, the MMH accounted for between 54 and 61% of all public patient deliveries in Brisbane (252). At the first antenatal visit, the MUSP sample was found to be representative of lower and middle SES women, with lower reported family income and lower status partner employment than the Brisbane average. The MUSP women, on average were younger and more likely to be single, but did not differ from private patients in obstetric outcomes or perinatal mortality (252). The sample was mainly Caucasian (91.8%), while also including Asians (3.7%), Maoris (1.8%) and Indigenous Australians (2.3%). Lifestyle characteristics showed that 51.1% of women had smoked before becoming pregnant; 40.1% reported having smoked the week before the antenatal visit, and 9.5% reported smoking 20 or more cigarettes per day. While 74.5% reported using alcohol before pregnancy, only 4% reported alcohol use in early pregnancy (252).

Subjects were selected into the study, independently of exposure status, and most measures subsequently obtained prospectively. Thus developmental and environmental risk factors were ascertained many years prior to assessment of psychopathology at 14 and 21 years. This is one of the many strengths of a prospective longitudinal study, as it helps establish temporality and limits recall bias related to memory, or based on knowledge of outcome status (253). However, lifetime and recent DSM-IV diagnoses were ascertained at 21 years.

Follow-ups and measurement ascertainment

To date, there have been five follow-up stages including:

(i) Baseline (N = 7,223): First Clinic Visit: Data focused on socio-demographics, maternal health behaviour and psychopathology;

(ii) Three-five days after birth (N = 7,223): a 103-item questionnaire including experiences over pregnancy; obstetricians extracted 200 items concerning the medical records of each pregnancy;

(iii) Six months after pregnancy (average age 6.5 months) (N = 6,720): a 103-item postal questionnaire which included questions on maternal psychopathology, social support and relationship quality and thoughts on their infant's development and medical needs;

(iv) Five years after pregnancy (average child age 5 year and 7 months) (N = 5,259): a 227-item questionnaire about themselves and their child, including for the first time valid and reliable measures of offspring behaviour problems, in addition to cognitive, social and motor development;

(v) Fourteen years after pregnancy (average adolescent age 13 years and 10 months) mother (N = 5,185) and child (N = 3,799) separate questionnaires including measures of offspring behaviour problems;

(vi) Twenty-one years after pregnancy (average young adult age 20 years and 7 months): mother (N = 3,691) and child (N = 3,809) separate questionnaires; offspring semi-structured psychiatric interview.

It is the last two follow-ups which involved self-reported or interview instruments taken directly from the offspring which form the psychopathological outcomes included in the current work (251). Table 3 in appendix 2 outlines the variables used in the study and ascertainment method, and tables 4 and 5 in appendix 2 present the summary statistics for the variables used in the current work. Importantly, how attrition may have affected the findings within each paper is included in supplementary analyses which can be found online (internet addresses are provided in chapters 4-7).

Outcome variables: psychiatric diagnoses at age 21

The DSM-IV disorders in the current work were diagnosed using the CIDI-Auto version 2.1 (254). The CIDI is a fully structured and comprehensive diagnostic interview for the assessment of mental disorders and provides diagnosis by computerised algorithms, with the questions eliciting symptoms and behaviours from respondents and mapping these to diagnostic criteria (255). It has strong inter-rater reliability and good test-retest reliability and an acceptable level of validity (255-257). The CIDI-Auto, which differs from the more common paper and pencil interview, was found to have good test-retest reliability during the drafting of the 2.1 version (255) and acceptable validity (258). The CIDI-Auto interviews were conducted between April 2002 and November 2004 with 2,575 participants, representing 35.7% of the original cohort. Interviews were conducted by trained interviewers, either at the MMH offices or the respondent's home, except for 25 respondents living outside Brisbane who completed the interview by telephone. The lifetime version of the CIDI was used, from which 12 month and 1 month diagnoses were also derived.

Life time and 12-month diagnoses were ascertained for PTSD, MDD, GAD, panic disorders, agoraphobias, social and specific phobias. Appendix 3 explains the structure of the interview for PTSD, GAD and MDD. See appendix 1 for descriptions of the other diagnoses. The comorbid diagnosis of MDD+GAD was constructed as outlined in paper 2, chapter 4, and partial PTSD was constructed as outlined in paper 1 chapter 7. Table 6 in appendix 2 provides prevalence estimates for diagnoses included in the current work. The prevalence of most disorders is comparable to the 12 month prevalence rates identified in the 2007 NSMHW survey (see appendix 1), including the increased risk of a psychiatric diagnosis for women. Lastly, section G of the CIDI assessed 23 psychotic experiences (15

delusions, 6 hallucinations, and 2 catatonias). Positive responses to delusions and hallucinations were probed to identify whether experiences were psychotic (catatonias were not used in the current work). These were used to construct a latent factor of psychotic experiences described below and illustrated in chapter 6.

Outcome variables: Self-report behaviour problems and depressive symptoms at ages 14 and 21

Psychiatric diagnoses are not the only way to measure psychopathology; self-reported behaviour problems can provide an effective means of studying the development of psychopathology in large, longitudinal samples. In the current work we use behaviour problems taken from Achenbach's Youth Self-Report (YSR) during adolescence and Young Adult Self-Report during early adulthood (259, 260). The items in these scales cover the spectrum of internalising and externalising syndromes. Internalising problems refer to over controlling symptoms directed inwards including depressive, anxious and somatic complaints, while externalising problems involve poorly controlled and outwardly directed symptoms such as aggressiveness and delinquency (261). While psychiatric diagnoses remain the primary focus of the current research, ongoing controversy surrounding the definitions and structural properties of these disorders (62) means the use of valid and reliable continuous, broad-band syndrome scales has a useful role in etiological research.

Achenbach System of Empirically Based Assessments (ASEBA)

The ASEBA is a collection of instruments designed to measure common behavioural and emotional problems across childhood, adolescence and early adulthood, occurring in the prior six months. At each of these three developmental stages, a different instrument is used including many similar items across ages, but termed in an age appropriate manner. At offspring age 5 years mothers completed the Child Behaviour Check List (CBCL) in relation

to their child's behaviour, at age 14 adolescents completed the Youth Self-Report (YSR) concerning their own behaviour, and at age 21 the young adults completed the Young Adult Self-report (YASR) concerning their own behaviour (259, 260, 262). The CBCL, YSR and YASR contain 113, 102 and 114 items respectively, with three possible responses to each item (not true/ somewhat true/ often true), and with the items summing to form a number of empirically derived narrow-band syndrome scales (anxious/depressed, withdrawn, delinquent, aggressive, attention, thought, social and somatic). However, the current work uses only the broadband syndromes of internalising and externalising behaviour problems from the YSR and YASR as outcomes variables (see tables 7 and 8 in appendix 2 for the included items, subscales, sample sizes and reliability estimates). The ASEBA scales have been used widely in clinical and general population samples and are found to have good reliability and validity (259, 260, 262-265). Further information on how the scales were operationalised and distributed in the sample is found in chapter 5 and appendix 2.

The CBCL was used in the current work not as an outcome variable but as a predictor of later psychopathology. It is included here for its relation to the YSR and YASR. Notably, mothers completed a shortened version of the CBCL designed to include the most commonly occurring behaviours in five year olds (265, 266), assessing 10 items each from the internalising and externalising scales, 10 items from the social/attention/thought sub-scales, and three additional items. Using a selected subsample of 76 parents at child age 5 years who completed the full version of the CBCL, the correlation between the full and short forms were: internalising = 0.89; externalising = 0.94; total behaviour problems = 0.98 (267).

Centres for Epidemiological Studies – Depression (CES-D) scale

At the 21 year follow-up, offspring depressive symptoms were measured using the Centres for Epidemiologic Studies Depression (CES-D) scale (268). The CES-D comprises 20

symptoms of negative and positive affect regarding the past week. The CES-D was constructed using well-known items from existing depression scales, correlates well with other depression scales, and has been found to have good internal consistency and good short-term test-retest reliability (268-270). See paper six for further information, and table 9 in appendix 2 for the symptoms list, sample size and reliability estimates.

Risk Factors

Fetal development

All obstetric data was taken from medical records, including birth weight, GA, parity and gender, with these measures available for all 7,223 participants. Birth weight z-scores adjusted for GA and gender were constructed to distinguish between babies who had experienced IUGR, from those who were small for reasons of gender or GA. This measure was constructed to replicate the predictor variable used in previous MUSP studies linking birth weight to mental health symptoms (108, 115):

$$\text{z-score of } \textit{birth weight} = (X_{\text{GA, Gender}} - \bar{X}_{\text{GA, Gender}}) \div S_{\text{GA, Gender}}$$

In the formula above, X is the observation, $\bar{X}$ and S are the mean and standard deviation, conditioned on GA and gender, respectively.

Maternal psychopathology

Maternal depressive and anxious symptoms were ascertained at every follow-up using the Delusions-States-Symptoms Inventory (DSSI), which includes sub-scales, both consisting of seven items designed to include the primary features of anxiety and depression (271) (table 10 appendix 2). The DSSI has been used extensively in community samples (272-274), and has been found to correlate well with other established symptoms scales including the Edinburgh Postnatal Depression Scales (EPDS) and the Hospital Anxiety/Depression Scale

(HADS) (275-277). Studies in the MUSP found that DSSI symptoms are separate to those which arise naturally throughout pregnancy (278), and the DSSI depression scale has been found to strongly correlate with DSM-IV MDD (279).

Maternal stress symptoms were ascertained at the first four time points of FCV (i.e. the prenatal measure), 3-5 days after birth and at child 6 months and 5 years of age, and were measured using the four-item Reeder Stress Inventory (RSI). The RSI was designed to measure self-perceived daily strain resulting from the physiological and psychological reactions to personal or social situations such as daily hassles, major events and coping resources (280, 281). A recent validation study has supported the construct validity of the RSI (282). The items can be found in chapter 5.

Maternal cumulative stressful life events

Maternal exposure to stressful life events was measured at birth in relation to events having taken place in the last six months of pregnancy, using eight items adapted from the Social Readjustment Rating Scale (SRRS) (283). The items included experience of death of a significant other, personal health problems, serious disagreements with partner or someone else, serious financial problems or problems with accommodation and partner having major employment change or a problem with the law. The SRRS contains a large number of events which indicate or require that the individual make a significant change to their ongoing life pattern, rather than measuring the emotional, psychological or social impact of the event. The SRRS is based on the belief that cumulative life stressors play a role in increasing the risk of many human illnesses (283). The SRRS is one of the most widely used instruments for measuring stress (284), including a recent investigation into suicide attempts (285).

Maternal prenatal vaginal infection

At birth, 7,118 mothers reported if they had experienced vaginal infection/discharge over pregnancy (did not happen/ minor problem/ moderate problem/ major problem).

Infant illness susceptibility

When offspring were aged 6 months, mothers were asked a series of questions regarding their child's health status and need of medical attention since birth including: a question of how many times medical attention had been sought for the infant (0/1/2/3-4/5+) and four questions regarding the frequency (never/rarely/monthly/weekly/often) of health problems possibly resulting from infection (vomiting, diarrhoea/constipation, skin rashes, cold/cough/runny nose), which were summed. We combined both variables into a single latent factor capturing the 'co-occurrence' of both items to represent infant illness susceptibility (n = 6,286).

Childhood cognitive ability

The Peabody Picture Vocabulary Test-Revised (PPVT-R) was administered to 3,999 children at the five year follow-up. The test requires the examinee to indicate which one of four pictures best describes a word which the examiner expresses verbally, with the resulting score providing a standardised measure of receptive vocabulary development that does not rely on expressive language skills (286). The PPVT-R has been validated against other standardised intelligence tests used on children (287-289).

Physical assault and polyvictimisation

The wording of the two responses which were coded as 'physical assault' were "were you ever seriously physically attacked or assaulted?" and "Have you ever been threatened with a weapon, help captive, or kidnapped?". Polyvictimisation was defined as the number of traumatic events experienced (1,2,3,4 or more).

Covariates

At the first clinic visit and 3-5 days after birth, mothers were asked how many cigarettes they usually smoked per day and how often and how much alcohol they consumed. Maternal age, parity and level of education, and maternal marital status were also collected at this time. At birth, Apgar score, forced induction of labour and offspring gender, were collected from obstetric records and mothers reported whether they had experienced pre-eclampsia during pregnancy and if the baby required "specialist medical care" after delivery. At the 5, 14 and 21 year follow-ups mothers were asked if their partner had seen a doctor because of a mental or emotional problem. The quality of the maternal relationship was assessed at birth using a shortened version of the Spanier Dyadic Adjustment Scale (DAS) (290). The scale has been found to have good reliability and validity in a number of cohort studies including the MUSP (266, 291, 292). The items, alpha and sample size are included in table 11 of appendix 2. Maternal contact with newborn was measured with a five-item index created for the MUSP, exploring the attitude of the mother towards her new born (items found in chapter 5). Because the majority of respondents indicated high levels of contact with baby and low levels of conflict with their partner, both variables were categorised with the two higher categories of each variables representing the extreme ends of the distribution (293).

Statistical analysis and modelling approaches

This section discusses the traditional statistical methods often employed in observational epidemiology in addition to the more advanced techniques and how these methods were applied to the current work. For more specific detail of the statistical modelling procedures used in specific analyses as well as information regarding sample sizes see chapters 4-7.

Multivariate logistic and linear regression

Multivariate linear regression is used to measure the association between a quantitative dependent variable Y with a number of independent variables X_1 to X_k:

$$Y = \alpha + \beta_1 X_1 + \beta_2 X_2 + \beta_k X_k + e$$

The α coefficient represents the intercept (predicted Y when the independent variables take on the value of 0), the β coefficient represents the amount by which Y is expected to change for a single unit change in X, and e is a random variable which represents the difference between observed and predicted values of Y. We make a number of key assumptions about the data: (i) Independence – the Y observations are statistically independent, conditionally on X; (ii) Linearity – the expected value of Y is a linear function of the independent variables, given values of the other independent variables; (iii) homoscedasticity – the variance of Y is the same for any combination of X_1 to X_k; and (iv) Normality of the error distribution – for any fixed combination of X_1 to X_k the variable e is Normally distributed. These assumptions were assessed in the current work, and transformations were used when quantitative dependent variables exhibited some skewness.

Multivariate logistic regression is used to measure the association between a binary dependent variable Y (0 = negative, 1= positive) with independent variables X_1 to X_k. The dependent variable is assumed to follow a binomial distribution, conditional upon values of the independent variables.

$$\log(\text{odds } Y = 1) = \alpha + \beta_1 X_1 + \beta_2 X_2 + \beta_k X_k + e$$

The left hand side of the equation represents the log odds that Y equals 1, the α coefficient represents the baseline odds (odds of the outcome in those without exposure status on the X's), the β coefficient represents the estimated exposure odds ratio for the respective X. A

number of issues were considered, including the use of independent observations, exploring non-linearity, and reducing multicollinearity (294, 295).

Extensions on logistic and linear regressions

Multinomial logistic regression is used to measure the association between a nominal (k > 2) dependent variable with independent variables X_1 to X_k, where the dependent variable follows a multinomial distribution conditional upon independent variable values. It extends logistic regression by estimating the effect of an exposure on the odds that the outcome is in a particular category:

$$\log \frac{(\text{odds } Y = j)}{(\text{odds } Y = j')} = \alpha_j + \beta_j X_1 + \beta_j X_2 + \beta_j X_k + e$$

The left hand side of the equation represents the log of the odds that an individual will be in category j (j = 1…k) of the outcome compared with the reference category (which is the first category j'). This is referred to as the generalised logit. The remaining parameters have similar interpretations to those in the logistic equation, except that the coefficients correspond to the categories being compared in the outcome (295). The current work used multinomial regression to predict the outcome of comorbid major depression and generalised anxiety (k = 4).

Ordinal logistic regression is used to measure the association between an ordinal (k > 2) dependent variable with independent variables X_1 to X_k. While multinomial regression models allow the most flexible approach to modelling the risk of the independent predictors at different levels of the outcome variable, it does not take into account the ordinal nature of the outcome resulting in a loss of precision (296).

$$\log \frac{(\text{odds } Y \geq j)}{(\text{odds } Y < j)} = \alpha_j + \beta_j X_1 + \beta_j X_2 + \beta_j X_k + e$$

The equation is similar to the multinomial model, except that the equality sign is replaced with an inequality, indicating that each category j (j = 1…k) in turn will be grouped with values higher than itself and compared with a grouping that includes all lower values of j. Like the multinomial model above, the intercept and slope coefficients are estimated separately for each level of the outcome (hence the slopes are non-proportional). This differs importantly from the proportional odds model (also called the cumulative logits model), for which the regression slopes are assumed to be equal at different levels of the outcome (295, 296). However, this method also differs from the multinomial model by allowing the main effects and interactions to be tested across the full range of the response variable (no PTSD, partial PTSD and full PTSD), rather than between two levels of the outcome.

Lastly, the current work employed polynomial and interaction terms:

$$Y = \alpha + \beta_1 X_1 + \beta_2 X_1^2 + e \quad (1) \qquad Y = \alpha + \beta_1 X_1 + \beta_2 X_2 + \beta_3 (X_1 \times X_2) + e \quad (2)$$

The final β coefficient in equation one is the quadratic expression of X_1, which was the highest order polynomial used in the current work to test for non-linear effects. Likelihood ratio tests were also used to test the non-linear associations between Y and ordinal categorical predictors (explained in the relevant papers). The final β coefficient in equation two is the multiplicative effect (interaction) of X_1 by X_2. Said differently, it assesses if the effect of X_1 on Y varies at different levels of X_2 (as the current work didn't test interactions between two quantitative variables). Such interactions played a role in a number of hypotheses, and are detailed further in the relevant paper. Because the partial proportional odds model includes a test of proportionality (parallelism) of the dependent variable, the interaction tests can be understood as a second-level interaction of the form $Y = X_{\text{outcome level}} \times X_{\text{trauma type}} \times X_{\text{gender}}$.

Structural Equation Modelling (SEM) for multidimensional latent outcomes

SEM could appropriately be called latent variable path analysis, and it is these two concepts which are briefly outlined here in relation to the current work. A manifest variable is one which can be directly observed and measured, while a latent variable is more abstract and instead must be constructed from a number of manifest 'indicator' variables (297). As an example, a latent variable could be a continuous score of paranoid thinking, of which one of several indicators could be the false belief that one was being tested or experimented on. While traditionally, indicators are combined *a priori* to form a 'composite' scale, accompanied by classic statistical tests to assess reliability, SEM takes a different approach by which latent variables are derived from the patterns of covariance among the indicators.

$$X_1 = b_1(F_1) + b_2(F_2) + \ldots b_p(F_p) + d_1(U_1)$$

The above simplified equation represents an Exploratory Factor Analysis (EFA). Each indicator variable from X_1 to X_k (X_1 shown) is the linear combination of the latent factors F_1 to F_p, with the regression slopes b_1 to b_p representing the factor loading, and with $d_1(U_1)$ representing the unique variance in X_1 not explained by the latent factors. Importantly, the indicators are 'explained' by the latent variables, meaning that the latent variable influences the indicators, rather than the reverse. Secondly, as factor analysis treats the latent variables as the predictors they are also able to correlate (equivalent to multivariate regression). Lastly, the separation of the unique variance from the variance explained by the hypothesised latent variables reduces the measurement error leading to a better specified construct (298).

In exploring the latent structure of psychotic experiences, the major issue concerns dimensionality and how best to model it. Recent investigations into the structure of positive psychotic experiences support a multidimensional structure, in which five separate but correlated factors represent hallucinations, paranoia, grandiosity, delusions and paranormal

beliefs (91, 299). The paranormal beliefs factor however was only represented by two indicators, and was strongly correlated with the delusions factors. Further, the current work did not include experiences of grandiosity, and included fewer items in total, thus it was expected that the structure in the current work would comprise of fewer but similar factors. Exploratory Factor Analysis (EFA) revealed that three factors had a superior fit to the data, with the factors representing hallucinations, delusions of paranoia and reference, and delusions of thought interference (bizarre and non-bizarre). The current work aimed to predict a general factor of psychotic experiences, similar to a recent study using a broader range of psychotic symptoms, which provided empirical support for a general psychosis factor which was found to explain the variance among five correlated dimensions (300).

Though largely equivalent (300-302) a bifactor model was chosen instead of a second-order model to represent the general factor of psychosis, as it had superior fit and because it is the best solution when it is unclear if a unidimensional or multidimensional representation best fits the data (i.e., large factor loadings on the unidimensional model), as the general (overall) factor is retained while specific factors (in this case paranoia/reference and thought interference) can also be modelled separately (301) (see table 1 and figure 1 in paper 2, chapter 6). Because the current work aimed *a priori* to predict a general construct of psychotic experiences, and because the bifactor and correlated three factor models differed little according to fit indices, we selected the bifactor model without performing χ^2 difference testing (see chapter 6 for technical details and statistical tests regarding the EFA and CFA steps).

Lastly, path analysis has a number of distinct advantages over regression analysis, particularly when using longitudinal data. Firstly, rather than simply regressing the outcome on all predictors, regression parameters can be constrained or unconstrained depending on the

hypothesis. Regarding the hypotheses in chapter six, this allowed the prenatal exposures to predict the outcome via a postnatal exposure without needing to include the direct effect. Secondly, this allowed the simple integration of indirect effects, which in Mplus includes the capacity to use resampling methods to test the significance of the indirect effect (303, 304). Thirdly, the easy manipulation of the parameters in path analysis makes it possible to test for moderation effects which are simple to interpret (305) (explained in chapter 6).

Longitudinal Mixture Modelling

This section outlines three concepts fundamental to the Latent Class Growth Analysis (LCGA) used in chapter five. Latent Class Analysis (LCA) is the qualitative latent variable analogue to factor analysis, by which subjects are sorted into groups depending on relationships among a number of indicator variables. Statistical independence means that the joint probability of A and B equals the product of their probabilities, written $P^{A_i B_j} = P^{A_i} \times P^{B_j}$. In the case where statistical independence does not hold, the dependency between A and B can be measured, for example as an odds ratio, or the dependency between A and B could potentially be explained by a third factor (in regression a confounding factor). In LCA however we introduce the latent variable X to explain the dependency between A and B. Put simply and extended to more than two manifest variables, LCA summarises the covariances among the manifest variables into a number of discrete categories within a single latent variable (306).

The second crucial concept is conventional growth curve modelling, by which a fixed effect models the sample's average 'growth' of an outcome over time (from repeated measures of the dependent variable), including constant, linear and higher order functions, and random effects are used to model individual variation from the average (307). An extension on this model is multi-group analysis, by which the sample can be divided into groups (often male

and female), with separate growth curves estimated in each group. Now, LCGA can most simply be explained as growth curve modelling in which the multiple groups are unobserved (latent) subpopulations determined by the data. Thus while heterogeneity in the sample is measured with random effects in the conventional approach, in LCGA the latent categorical variable allows different growth trajectories to vary around different means. While it is possible to include random effects within the classes of the latent variable, an approach known as generalized mixture modelling, the current work used the semi-parametric technique of LCGA which assumes the variance and covariance of growth factors within classes are zero (for reasons outlined in chapter five) (308, 309).

With regard to the work contained in chapter five, before constructing the trajectories, the scores on each scale at each time point were summed and dichotomized with the highest scoring 10% of individuals defined as cases, ensuring that the concept of case remained stable across time. Next, Latent Class Growth Analysis (LCGA) was used to determine the optimal number of groups (classes) and the profiles of depressive, anxious and stress symptoms in these groups, 'contained' in the data. Though the methods used to derive the trajectories differed between the two articles contained in chapter five (it was found necessary to impute missing values of depression, anxiety and stress in the latter paper), the results were very similar. In both cases LCGA identified seven trajectories including: (1) depressive, anxious and stress symptoms during pregnancy (i.e., the prenatal group), (2) during birth, (3) at 6 months, and (4) at 5 years. In addition to (5) ongoing depressive, anxious and stress over the entire period, (6) ongoing stress symptoms (only) over the entire period, and (7) a normative group (see the first figure in both papers contained in chapter five). Lastly, it is important to note that the prenatal measures of anxiety and depression were also frequently used as covariables in the other analyses (see chapter 5 for technical details and statistical tests regarding the LCGA).

Statististical approaches dealing with sample attrition

Multivariate logistic regression for attrition

The primary method used to deal with attrition has been multivariable logistic regression analysis, in which the binary outcome variable compares the odds of being included in the study versus not being included in the study by a number of baseline measures. This simple method allows the researcher and consumer to observe which variables have been lost in a biased manner and judge how this may affect the studies generalisability.

Inverse probability weights (IPW) analysis

From the multivariate logistic regression model described above it is possible to produce weights representing the inverse probability of each participant being included in the study. The analysis is then repeated using these weights.

Multivariate multiple imputations (MMI) analysis

Multivariate multiple imputations is a more complex method. This method creates a number of imputed datasets, each with unique imputed values randomly generated for the missing values to fully account for variability in the missing data, based on a series of predictive equations fitted to the observed data and applied to predict missing values. Each imputed datasets is then analysed to obtain a corresponding set of estimates of interest. Results are then pooled to obtain adjusted estimates. These may be compared to the results of the non-imputed analyses (310). These methods are detailed further in relation to the main findings in the following sections.

Chapter 4 - Fetal Origins of Psychopathology

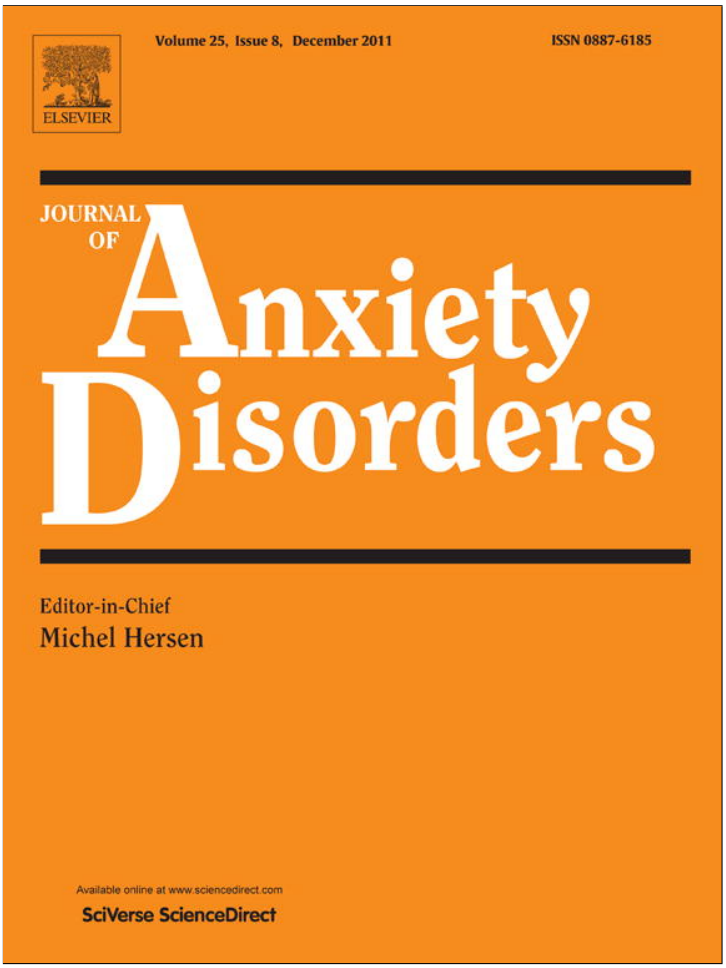
The association between lower birth weight and anxiety disorders in young adult offspring

Published manuscript and formal citation

Betts, K. S., Williams, G. M., Najman, J. M. & Alati, R. (2011). The association between birth weight and anxiety disorders in young adults. *J Anxiety Disord* 25, 1060-7.

Study purpose: This paper was designed to fill a gap in the literature at the time by which most investigations into the link between fetal development and later offspring psychopathology had not investigated specific psychiatric outcomes of anxiety disorders but rather relied on broad-based measures or aggregated DSM disorders.

Supplementary material: Some information relevant to this study (i.e., attrition, IPW and MMI analyses) was published online in a supplementary section only and can be accessed at: http://www.sciencedirect.com/science/article/pii/S0887618511001216



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The association between birth weight and anxiety disorders in young adults

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ABSTRACT

Recent evidence has linked birth weight to later behaviour/mental disorders, yet studies have hitherto neglected to investigate the relationship between birth weight and adult anxiety disorders. Prospectively collected data from 2210 mother/offspring pairs of the Mater University Study of Pregnancy (MUSP) birth cohort was used to test for associations between birth weight *z*-score and four major groupings of DSM-IV anxiety disorders. Birth weight *z*-score was linearly and inversely associated with lifetime diagnosis of post-traumatic stress disorders at 21 years, with those falling within the smallest birth weight quintile group at almost two-fold increased odds (OR = 1.96, 95% CI: 1.10, 3.52) of being diagnosed with the disorder compared to those falling within the largest group. The association remained when subsequent analysis restricted the sample to those exposed to trauma. This is the first study in which birth weight has been found to be associated with post-traumatic stress disorders in adults.

1. Introduction

Evidence from a range of scientific disciplines show that organisms are capable of responding to environmental cues during a critical period of development in an attempt to adapt characteristics better suited to environmental conditions, a process which in humans results in permanent changes that may have pathological consequences in later life (Bateson et al., 2004). Due to the pioneering work of Barker (2004), this has come to be known as the developmental origins of adult disease. The findings presented in numerous reviews across a number of disciplines provide evidence linking altered fetal development to later adult diseases including cardiovascular disease, hypertension, obesity and diabetes type 2 (Warner & Ozanne, 2010). Despite this, few studies have tested the potential role that altered fetal development may have on the later development of mental health disorders.

The majority (Alati et al., 2007; Cheung, Khoo, Karlberg, & Machin, 2002; Gale & Martyn, 2004; Herva et al., 2008; Nomura et al., 2007; Patton, Coffey, Carlin, Olsson, & Morley, 2004; Raikkonen et al., 2007; Wiles, Peters, Leon, & Lewis, 2005), though not all (Osler, Nordentoft, & Andersen, 2005; Vasiliadis, Gilman, & Buka, 2008) of the studies which have tested the relationship between birth weight and mental health symptoms have found small but robust associations with symptoms of distress (Cheung et al., 2002; Raikkonen et al., 2007; Wiles et al., 2005), depression (Alati et al., 2007; Gale & Martyn, 2004; Herva et al., 2008; Patton et al., 2004) and/or anxiety (Nomura et al., 2007). Studies exploring broader behavioural outcomes have found associations between birth weight and stress susceptibility (Nilsson, Nyberg, & Ostergren, 2001) and depressive and anxious symptoms (Alati et al., 2009; Hack et al., 2004, 2009). There is also evidence of no associations (Wiles et al., 2006), and effect modification due to socio-economic factors (Kelly, Nazroo, McMunn, Boreham, & Marmot, 2001). Additional inconsistencies include the nature of the trend, with some reporting inverse, linear associations (Alati et al., 2007; Cheung et al., 2002; Gale & Martyn, 2004; Kelly et al., 2001; Nomura et al., 2007) and others reporting non-linear, reverse J-shaped associations (Alati et al., 2009; Nilsson et al., 2001). Finally, some studies report that birth weight is predictive of later behaviour/mental health problems in females only (Alati et al., 2007; Hack et al., 2004, 2009).

Despite the existing research into the developmental origins hypothesis, the association of birth weight with adult anxiety disorder diagnosis has yet to be tested using data from a birth cohort. In two earlier studies using the Mater University Study of Pregnancy (MUSP) cohort, we found associations between birth weight and anxious/depressive symptoms at child age 14 (Alati et al., 2009) and depressive symptoms in female offspring at age 21 (Alati et al.,

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2007). The present study aimed to test associations between birth weight and four DSM-IV anxiety disorders, specifically Generalised Anxiety Disorders (GAD), phobias, Panic Disorders (PD), and Post-Traumatic Stress Disorders (PTSD) in young adults.

2. Materials and methods

2.1. Participants

The sampling frame of the MUSP included all pregnant public patients attending consecutive obstetric clinic visits at the Mater Misericordiae Hospital (MMH) in Brisbane between 1981 and 1984. Admission on the grounds of attending a public consultation led to a sample skewed to lower income women, greater detail on the MUSP research design, participants and data collection phases have been described in detail elsewhere (Najman et al., 2005). At baseline, the sample for this study consisted of 6433 Caucasian women and their offspring (52% male). This study restricted all analysis to the Caucasian group, as ethnicity was associated with birth weight, and the need to adjust for the small numbers of non-Caucasians (5% of the 21 year sample) was more easily addressed by exclusion. At age 21 there were 2210 mothers and their offspring with complete data on all variables of interest.

2.2. Measurement of anxiety disorders

Anxiety disorders were measured at the 21 year follow-up using the lifetime version of the Composite International Diagnostic Interview (CIDI-Auto) version 2.1 (World Health Organisation, 1997). The CIDI-Auto is a computerised instrument which was administered by a trained interviewer, and has good validity and inter-rater and test-retest reliability (Peters, Clark, & Carroll, 1998). Anxiety disorders were diagnosed according to the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV) (First and Tasman, 2004), for the following selected disorders; Panic Disorders (PD), phobias, Generalised Anxiety Disorders (GAD), and Post-Traumatic Stress Disorders (PTSD). To gain a diagnosis of PTSD participants had to nominate one or more of the eleven possible traumatic events included in the CIDI as having occurred to them in their life time. We combined all trauma events and created two binary variables: life time trauma exposure and 12 month trauma exposure (both coded yes/no). Twelve month and life time diagnoses were made for each of the 2563 (35%) individuals who completed the CIDI-Auto using standard computer algorithms. An age at onset was also elicited from those who met the criteria for these mental disorders.

2.3. Predictors and confounders

Birth weight, gender and gestational age in weeks (GA) were extracted from hospital obstetric records at the time the child was born. As in previous papers (Alati et al., 2007, 2009), fetal growth rate was estimated by calculating birth weight *z*-scores, internally adjusted for gender and GA. The *z*-score was calculated by subtracting from an individual's birth weight, the mean birth weight from all other participants with the same GA and gender, and then dividing by the birth weight standard deviation specific to those with the same GA and gender. In this study, the *z*-score was used both as a continuous variable and split into quintile groups so that the odds of being diagnosed with an anxiety disorder could be observed in each quintile group compared to a reference quintile group (quintile group 1 = smallest *z*-score group, quintile group 5 = highest *z*-score group).

At the first antenatal clinic visit (FCV) maternal smoking was recorded (non-smoker, smoker, heavy smoker) along with maternal alcohol use (abstainer, 0–0.5 drinks/day, 0.5–1.0 drinks/day, >1 drinks/day) during pregnancy. At this time, the Delusions-States-Symptoms Inventory (DSSI) (Bedford & Folds, 1977) assessed maternal antenatal anxiety symptoms (non-anxious, anxious). The DSSI anxiety subscale consists of seven items constructed to include the primary features of an anxiety disorder. The DSSI has been found to correlate well with other established symptoms scales, such as the Edinburgh Postnatal Depression Scale (EPDS) and the Hospital Anxiety/Depression Scale (HADS) (Bedford & Deary, 1999).

At birth, maternal age (13–19, 20–34, ≥35) and parity (0, 1–2, ≥3) were taken, along with the infants' birth weight and gestational age. Concurrent measures of offspring socio-economic position (SEP) were taken at the 21 year follow-up which included offspring income (low, middle, high) and offspring work type (non-manual, manual, student, other/unemployed), along with offspring cigarette use per day (none, 1–19, ≥20) at 21, included as a lifestyle indicator.

2.4. Statistical analysis

All analyses were carried out on a total of 2210 Caucasian mothers and their offspring, all of which had complete data on all measures of interest. Three Phobias including agoraphobias, social phobias and specific phobias were combined into one group (phobias). Logistic regression was used to determine the univariable associations of the birth weight *z*-score quintile groups with both life time and 12 month diagnosis of the four anxiety disorder categories and also to explore the univariable associations between the DSM-IV lifetime disorders and possible confounding factors.

Multivariable logistic regression analysis included adjustment for maternal factors during pregnancy: smoking and alcohol consumption, maternal antenatal anxiety which has been found to be related with both lower birth weight and pre-term delivery (Pritchard & Teo, 1994) and offspring behavioural/mental health problems (O'Connor, Heron, Golding, & Glover, 2003), maternal age at birth and parity. Concurrent measures of offspring SEP and lifestyle, such as income, work type patterns and smoking status were also included in the fully adjusted model. As we found birth weight was associated with a diagnosis of PTSD, which requires exposure to a traumatic event, we conducted additional analyses. Firstly we investigated whether birth weight was associated with trauma exposure. Then, we restricted the sample to those exposed to trauma ($n = 1136$) by excluding those who did not report experiencing a traumatic event. We repeated univariable and multivariable logistic regression analyses to investigate whether birth weight predicted PTSD diagnosis among trauma exposed participants odds ratios and 95% confidence intervals (95% CI) are presented for the unadjusted and fully adjusted models.

For disorders which were found to be associated with birth weight, gender was tested as an effect modifier. We also conducted unadjusted and adjusted Cox regression analysis to estimate hazard ratios (HR) of receiving an anxiety disorder diagnosis with 95% CI. We used likelihood ratio tests to test for linearity (by entering birth weight *z*-score into all models as a continuous variable), and quadratic terms to test for non-linear associations. All analyses were conducted using STATA 11 (STATA Corp LP).

2.5. Adjustment for attrition

The participants in the analysis represented 35% of the original cohort restricted to Caucasian participants ($n = 6433$). In order to determine if differential loss to follow-up was likely to have biased the results of the study, we fitted a multivariate logistic regression model to compare a number of baseline factors between those who were still in the study and those that were lost to follow-up.

Starting from a missing at random (MAR) assumption (Sterne et al., 2009) we used the STATA procedure of multiple imputation,

Table 1
Multivariate attrition analysis – showing the likelihood of *not* being lost to follow-up according to baseline factors and restricted to Caucasians [expressed as OR with 95% confidence intervals (CI) (n = 5946)].

Effect	OR (95% CI)	*P*-value*	*P* for LRT**
Antenatal anxiety	*Reference: no*		
Yes	0.69 (0.58, 0.83)	<0.001	<0.001
Smoking FCV	*Reference: none*		
Smoker	0.89 (0.79, 1.01)	0.07	
Heavy smoker	0.79 (0.63, 0.98)	0.03	0.04
Alcohol FCV	*Reference: none*		
0–0.5 drinks/day	1.13 (1.01, 1.26)	0.03	
0.5–1 drinks/day	0.83 (0.58, 1.18)	0.30	
>1 drinks/day	0.92 (0.57, 1.51)	0.75	0.07
Maternal age at birth	*Reference: ≥35*		
13–19	0.66 (0.48, 0.91)	0.01	
20–34	0.83 (0.63, 1.09)	0.18	0.02
Family income FCV	*Reference: $26,000+*		
$0–5199/week	0.54 (0.37, 0.79)	0.002	
$5200–15,599	0.74 (0.55, 0.98)	0.04	
$15,600–25,999	0.75 (0.56, 1.01)	0.06	0.02
Previous births	*Reference: none*		
One or two	0.93 (0.82, 1.05)	0.25	
Three or more	0.74 (0.60, 0.91)	0.004	0.01
Offspring gender	*Reference: male*		
Female	1.28 (1.15, 1.43)	<0.001	<0.001
Birth weight *z*-score	*Reference: quintile 5*		
Quintile 1	0.99 (0.83, 1.17)	0.87	
Quintile 2	0.99 (0.83, 1.17)	0.88	
Quintile 3	1.16 (0.98, 1.37)	0.09	
Quintile 4	1.13 (0.96, 1.34)	0.15	0.15
Partner status at FCV	*Reference: single*		
Married	0.78 (0.60, 1.02)	0.07	
Living together	1.19 (0.94, 1.50)	0.15	
Separated–widowed–divorced	0.58 (0.37, 0.92)	0.02	<0.001

* *P*-value for the coefficient.
** *P*-value for the likelihood ratio test (LRT).

with 10 cycles of regression switching to generate 10 imputation data sets and repeated our analysis using these data sets. Variables used in the imputation models included maternal alcohol and tobacco use, indicators of maternal socioeconomic position, birth weight, gestational age, mother's education, anxiety, depression, parity and concurrent measures of offspring work type, offspring income and offspring smoking at 21 years.

3. Results

The birth weight *z*-scores were calculated using parameters from the baseline offspring sample (n = 7223) including birth weight in grams (mean = 3385.74, SD = 518.78), gestational age in weeks (mean = 39.42, SD = 1.68) and gender (male = 51.89%). This was done so that we were able to compare the *z*-scores of the baseline sample with the remaining *z*-scores in the sample used in our analyses (n = 2210) to examine how attrition may have affected our predictor variable (the prevalence estimates of the anxiety disorders by *z*-score quintile group is also shown in Table 2).

Table 1 shows the odds (as odds ratios with 95% CI) that an individual was included in the study in relation to a number of baseline factors, with all factors adjusted for one another. Those lost to follow-up were more likely to be born of mothers who were young, who smoked and were anxious during pregnancy. Despite this, the two groups did not differ significantly in relation to our main predictor variable, and the LR statistic also showed that birth weight was not subject to significant differential attrition.

Tables 2 and 3 show univariable associations between birth weight and life time and 12 month anxiety disorders (Table 2), and life time anxiety disorders and potential confounding factors (Table 3). Birth weight *z*-score was linearly associated with PTSD and those in the lowest *z*-score group had increased odds of life time and 12 month PTSD diagnosis relative to the highest *z*-score group (quintile group 5). Maternal smoking, offspring gender, and offspring's own smoking status at 21 years of age were associated with life time anxiety disorders. Maternal antenatal anxiety was associated with PD and phobias.

In fully adjusted analysis, birth weight remained linearly associated with life time PTSD diagnosis (Table 4). Those in the lowest *z*-score group were at almost twice the risk of receiving a life time diagnosis of PTSD compared with those in the highest *z*-score group. For those who received a diagnosis in the previous 12 months, the point estimates were almost the same as those obtained for PTSD life time, suggesting that failure to observe a statistically significant association may be due to lack of statistical power to detect a difference. We found no evidence of non-linearity in unadjusted or adjusted associations between birth weight and anxiety disorders. Results remained virtually the same when we repeated all analysis using the disaggregated phobias (agoraphobias, social phobias and specific phobias). Results from Cox regression analysis were consistent with those presented here (see supplementary Table 1).

Table 5 shows associations between birth weight *z*-score and PTSD in participants who had experienced exposure to trauma. Results were very similar to those which included all participants (Table 4). Further, birth weight *z*-score was not associated with trauma exposure in the complete case analysis (n = 2210), with no significant increase of exposure to trauma among participants in the lowest *z*-score quintile group relative to those in the highest *z*-score quintile group in fully adjusted analysis (OR = 1.27, 95% CI: 0.96, 1.69). Nor was birth weight *z*-score as a continuous variable associated with trauma exposure in fully adjusted analysis (OR 0.93, 95% CI: 0.85, 1.02), suggesting that the relationship between birth weight and PTSD is not statistically accounted for by exposure to trauma.

When birth weight *z*-score by gender interaction terms were introduced into the adjusted models predicting PTSD no significant gender differences were found (PTSD life time P = 0.394). Multiple imputation analysis yielded the same results as those presented here (see supplementary Table 2).

4. Discussion

4.1. Principal findings

This study found no significant associations with DSM-IV anxiety disorders such as GAD, phobias and PD at 21 years. However, we found that birth weight *z*-score was linearly and inversely associated with DSM-IV life time PTSD diagnosis. Those falling in the lowest *z*-score quintile group were at almost two-fold increased risk of being diagnosed with life time DSM-IV PTSD compared with those in the largest *z*-score quintile group. Similar associations between birth weight *z*-score and PTSD were observed when those who had not been exposed to trauma were excluded from the analysis. In contrast to previous studies, we found no gender interaction in the association between birth weight and PTSD.

4.2. Comparisons with previous studies

To our knowledge, this is the first study to report an association between birth weight and PTSD. While previous studies have found associations with behaviour/mental health symptoms, this study used categories consistent with specific diagnostic criteria and was therefore able to distinguish between different anxiety disorders. This increased specificity could explain why life time PTSD was strongly associated with birth weight, while no associations were found with the other disorders. Hence, while it

Table 2
Univariable associations between birth weight *z*-score quintiles and lifetime and 12 month DSM-IV anxiety disorders at age 21 years [expressed in OR with 95% confidence intervals (CI)] (complete case analysis $n = 2210$).

BWT quintiles	PD		Phobias		GAD		PTSD	
	Prevalence (*n*/%)	Unadjusted OR (95% CI)	Prevalence (*n*/%)	Unadjusted OR (95% CI)	Prevalence (*n*/%)	Unadjusted OR (95% CI)	Prevalence (*n*/%)	Unadjusted OR (95% CI)
Birth weight *z*-score quintiles and lifetime DSM-IV anxiety disorders at age 21 years								
Quintile 1	20/4.12%	0.89 (0.42, 1.88)	93/6.39%	1.13 (0.80, 1.60)	19/3.92%	1.46 (0.70, 3.05)	45/9.39%	2.21 (1.26, 3.87)
Quintile 2	21/4.28%	1.26 (0.64, 2.48)	103/7.18%	1.25 (0.89, 1.76)	28/5.74%	1.99 (1.00, 3.97)	31/6.35%	1.45 (0.80, 2.62)
Quintile 3	20/3.72%	0.89 (0.44, 1.83)	94/6.50%	1.05 (0.75, 1.48)	30/5.59%	1.73 (0.86, 3.45)	34/6.37%	1.67 (0.95, 2.95)
Quintile 4	14/2.62%	0.70 (0.33, 1.50)	100/6.93%	1.08 (0.77, 1.51)	23/4.32%	1.39 (0.68, 2.86)	27/5.10%	1.14 (0.62, 2.09)
Quintile 5	17/3.25%	1	91/6.30%	1	14/2.68%	1	24/4.64%	1
OR for linear		1.01 (0.80, 1.28)		0.98 (0.88, 1.10)		0.91 (0.74, 1.13)		0.77 (0.65, 0.93)
P for linear		0.94		0.79		0.41		0.005
P for quadratic		0.97		0.71		0.12		0.36
Birth weight *z*-score quintiles and 12 month DSM-IV anxiety disorders at age 21 years								
Quintile 1	14/2.89%	0.90 (0.37, 2.20)	68/4.67%	1.02 (0.69, 1.50)	9/1.86%	1.67 (0.60, 4.74)	30/6.26%	2.12 (1.09, 4.13)
Quintile 2	16/3.26%	1.45 (0.66, 3.29)	73/5.09%	1.08 (0.74, 1.58)	10/2.05%	1.59 (0.56, 4.50)	21/4.30%	1.44 (0.71, 2.92)
Quintile 3	15/3.26%	0.95 (0.41, 2.22)	75/5.18%	1.08 (0.74, 1.56)	19/3.54%	2.60 (1.01, 6.71)	33/4.31%	1.60 (0.81, 3.15)
Quintile 4	11/2.06%	0.85 (0.36, 2.03)	77/5.34%	1.02 (0.70, 1.49)	17/3.19%	2.07 (0.78, 5.50)	21/3.97%	1.36 (0.68, 2.73)
Quintile 5	12/2.29%	1	73/5.06%	1	6/1.15%	1	16/3.09%	1
OR for linear		0.97 (0.74, 1.28)		1.01 (0.89, 1.14)		0.95 (0.72, 1.26)		0.78 (0.63, 0.96)
P for linear		0.83		0.91		0.73		0.02
P for quadratic		0.80		0.28		0.15		0.30

Table 3
Univariable associations between lifetime DSM-IV anxiety disorders and confounding factors [expressed in OR with 95% confidence intervals (CI)].

DSM-IV Life time diagnosis	Prevelence	PD OR (95% CI)	Phobias OR (95% CI)	GAD OR (95% CI)	PTSD OR (95% CI)
Antenatal anxiety	(*n* = *2210*)				
No	90.72% (*n* = 2005)				
Yes	9.28% (*n* = 205)	2.56 (1.43, 4.59)	1.42 (1.01, 2.00)	1.72 (0.96, 3.09)	1.55 (0.93, 2.57)
Smoking FCV	(*n* = *2210*)				
Non smoker	65.66% (*n* = 1451)				
Smoker	27.42% (*n* = 606)	2.00 (1.24, 3.25)	1.84 (1.46, 2.33)	1.21 (0.76, 1.90)	1.70 (1.17, 2.47)
Heavy smoker	6.92% (*n* = 153)	1.52 (0.63, 3.65)	2.43 (1.67, 3.54)	1.50 (0.73, 3.09)	2.84 (1.68, 4.80)
Alcohol use FCV	(*n* = *2210*)				
Non drinker	46.83% (*n* = 1035)				
0–0.5 drinks/day	49.86% (*n* = 1102	0.84 (0.52, 1.34)	0.81 (0.65, 1.01)	0.75 (0.49, 1.13)	1.01 (0.72, 1.42)
0.5–1 drinks/day	2.13% (*n* = 47)	1.17 (0.27, 4.99)	0.80 (0.37, 1.74)	0.86 (0.20, 3.63)	0.64 (0.15, 2.70)
>1 drinks/day	1.18% (*n* = 26)	1.05 (0.14, 7.95)	0.93 (0.35, 2.49)	1.16 (0.37, 6.99)	1.20 (0.28, 5.20)
Previous births	(*n* = *2210*)				
None	41.18% (*n* = 910)				
One or two	46.87% (*n* = 1080)	0.95 (0.58, 1.55)	1.00 (0.80, 1.26)	0.90 (0.58, 1.39)	1.07 (0.75, 1.54)
Three or more	9.95% (*n* = 220)	1.21 (0.57, 2.58)	1.00 (0.68, 1.46)	1.12 (0.56, 2.21)	1.20 (0.67, 2.23)
Gender	(*n* = *2210*)				
Male	47.74% (*n* = 1055)				
Female	52.26% (*n* = 1155)	3.50 (2.00, 6.11)	3.39 (2.66, 4.32)	2.42 (1.54, 3.81)	2.58 (1.77, 3.76)
Maternal age FCV	(*n* = *2210*)				
13–19	13.76% (*n* = 304)				
20–34	81.63% (*n* = 1804)	0.66 (0.36, 1.21)	0.71 (0.53, 0.95)	0.81 (0.46, 1.44)	0.57 (0.37, 0.87)
35+	4.62% (*n* = 102)	1.07 (0.37, 3.04)	0.90 (0.53, 1.55)	1.64 (0.67, 3.99)	0.67 (0.29, 1.59)
Offspring smoking	(*n* = *2210*)				
Non-smoker	63.30% (*n* = 1399)				
Smoker	30.68% (*n* = 678)	2.05 (1.26, 3.35)	1.95 (1.56, 2.45)	1.61 (1.05, 2.47)	2.99 (2.08, 4.30)
Heavy smoker	6.02% (*n* = 133)	2.57 (1.16, 5.67)	1.58 (1.02, 2.44)	1.25 (0.53, 2.97)	2.87 (1.55, 5.32)
Offspring work type	(*n* = *2210*)				
Non-manual	43.08% (*n* = 952)				
Manual	34.48% (*n* = 762)	0.30 (0.15, 0.57)	0.58 (0.45, 0.75)	0.49 (0.30, 0.80)	0.70 (0.47, 1.04)
Student	18.46% (*n* = 408)	0.77 (0.39, 1.32)	0.71 (0.52, 0.96)	0.44 (0.23, 0.84)	0.68 (0.41, 1.13)
Unemployed/other	3.98% (*n* = 88)	1.21 (0.47, 3.14)	1.65 (1.03, 2.65)	0.95 (0.37, 2.42)	1.99 (1.03, 3.83)
Offspring income	(*n* = *2210*)				
High	19.37% (*n* = 428)				
Middle	35.97% (*n* = 795)	1.07 (0.52, 2.05)	1.18 (0.86, 1.63)	1.05 (0.56, 1.93)	1.08 (0.65, 1.79)
Low	44.66% (*n* = 987)	1.24 (0.65, 2.36)	1.45 (1.07, 1.96)	1.35 (0.76, 2.39)	1.30 (0.81, 2.10)

is important to explicitly acknowledge that the specific association we found with PTSD may be a chance finding, it is also possible that associations found in previous studies between birth weight and DSM-IV 'any anxiety disorder' (Nomura et al., 2007), anxious/depressive behaviour subscales (Alati et al., 2009; Hack et al., 2004) or generalised anxiety symptoms (Hack et al., 2009) were due to participants with PTSD being included in these unspecific categories. Inconsistencies between our findings and the few available comparable studies may also be due to different research and methodological designs: one of these studies used a case-control research design (Nomura et al., 2007) and two used a dichotomized birth weight variable comparing normal birth weight children with very low birth weight children (Hack et al., 2004) and extremely low birth weight children (Hack et al., 2009).

While this is the first time an association has been found between birth weight and PTSD in a large birth cohort of this kind, a similar association has been suggested in a small study of 117

Table 4
Multivariate associations between birth weight *z*-score quintiles and lifetime and 12 month DSM-IV anxiety disorders at age 21 years [expressed in OR with 95% confidence intervals (CI)] (complete case analysis *n* = 2210).

BWT	PD	Phobias[a]	GAD[a]	PTSD[a]
Multivariable associations between birth weight *z*-score and lifetime DSM-IV anxiety disorders at age 21 years				
Quintile 1	0.84 (0.39, 1.83)	0.95 (0.66, 1.37)	1.45 (0.68, 3.08)	1.96 (1.10, 3.52)
Quintile 2	1.24 (0.62, 2.49)	1.16 (0.81, 1.64)	2.07 (1.03, 4.17)	1.33 (0.72, 2.44)
Quintile 3	0.91 (0.44, 1.89)	1.02 (0.71, 1.44)	1.83 (0.91, 3.70)	1.66 (0.93, 2.96)
Quintile 4	0.65 (0.30, 1.42)	1.03 (0.72, 1.45)	1.38 (0.67, 2.85)	1.07 (0.58, 1.99)
Quintile 5	1	1	1	1
OR for linear	1.03 (0.80, 1.31)	1.04 (0.93, 1.17)	0.91 (0.73, 1.13)	0.81 (0.67, 0.97)
P for linear	0.84	0.47	0.42	0.03
P for quadratic	0.94	0.42	0.09	0.53
Multivariable associations between birth weight *z*-score and 12 month DSM-IV anxiety disorders at age 21 year				
Quintile 1	0.81 (0.32, 2.04)	0.86 (0.57, 1.30)	1.69 (0.58, 4.92)	1.91 (0.96, 3.81)
Quintile 2	1.42 (0.63, 3.19)	1.00 (0.67, 1.48)	1.60 (0.55, 4.57)	1.32 (0.65, 2.71)
Quintile 3	0.96 (0.41, 2.28)	1.06 (0.72, 1.56)	2.82 (1.08, 7.37)	1.56 (0.78, 3.11)
Quintile 4	0.80 (0.33, 1.92)	0.98 (0.67, 1.44)	2.03 (0.76, 5.43)	1.27 (0.63, 2.57)
Quintile 5	1	1	1	1
OR for linear	1.00 (0.75, 1.32)	1.06 (0.93, 1.21)	0.94 (0.70, 1.26)	0.80 (0.65, 1.00)
P for linear	0.97	0.37	0.70	0.51
P for quadratic	0.66	0.15	0.14	0.41

[a] Adjusted for maternal smoking, maternal alcohol use, maternal anxiety, maternal age at birth and parity, offspring work type, income and smoking at 21 years.

Table 5
Multivariate associations between birth weight *z*-score quintiles and lifetime and 12 month DSM-IV post-traumatic stress disorder at age 21 years among participants exposed to trauma [expressed in OR with 95% confidence intervals (CI)] (complete case analysis $n = 1136$).

BWT	PTSD life time			PTSD 12 month		
	Prevalence (*n*/%)	Unadjusted OR (95% CI)	Adjusted[a] OR (95% CI)	Prevalence (*n*/%)	Unadjusted OR (95% CI)	Adjusted[a] OR (95% CI)
Multivariable associations between birth weight *z*-score and life time and 12 month DSM-IV PTSD among participants exposed to trauma at 21 years						
Quintile 1	38/16.89%	1.91 (1.07, 3.40)	1.87 (1.02, 3.44)	26/11.56%	1.81 (0.92, 3.57)	1.88 (0.93, 3.82)
Quintile 2	28/12.50%	1.34 (0.73, 2.47)	1.35 (0.72, 2.52)	19/8.48%	1.28 (0.63, 2.63)	1.33 (0.64, 2.78)
Quintile 3	34/14.17%	1.55 (0.86, 2.79)	1.69 (0.92, 3.10)	23/9.58%	1.47 (0.74, 2.93)	1.60 (0.78, 3.25)
Quintile 4	24/10.04%	1.05 (0.56, 1.96)	1.07 (0.57, 2.04)	20/8.37%	1.27 (0.62, 2.57)	1.28 (0.62, 2.64)
Quintile 5	20/9.62%	1	1	14/6.73%	1	1
OR for linear		0.80 (0.67, 0.97)	0.82 (0.68, 1.00)		0.81 (0.65, 1.01)	0.81 (0.65, 1.02)
P for linear		0.02	0.049		0.06	0.07
P for quadratic		0.27	0.52		0.22	0.409

[a] Adjusted for maternal smoking, maternal alcohol use, maternal anxiety, maternal age at birth and parity, offspring work type, income and smoking at 21 years.

severely maltreated children, where a birth weight below 2.25 kg was also found to predict PTSD (Famularo & Fenton, 1994).

We found that birth weight and PTSD were linearly associated, which compares well with existing studies, including an earlier study using the MUSP cohort (Alati et al., 2007). The addition of antenatal maternal anxiety had a negligible effect on all associations, and this is consistent with earlier studies where anxious status during pregnancy did not attenuate point estimates linking fetal growth with anxious depressive symptoms (Alati et al., 2007, 2009). It is possible that our failure to replicate a gender interaction as consistent with an earlier study using MUSP data (Alati et al., 2007) may be due to the reduced power resulting from the larger loss to follow-up associated with the CIDI interview compared to other less resource intensive measures.

4.3. Possible mechanisms

Underlying the developmental origins of adult mental health disorders is altered fetal hypothalamic-pituitary–adrenal (HPA) axis functioning, which once programmed *in utero* persists into extrauterine life. Animal models reveal that HPA axis dysregulation results from maternal nutrient restriction (Lingas & Matthews, 2001) and placental insufficiency, mediated via altered maternal HPA axis functioning (Lingas, Dean, & Matthews, 1999). In humans, increased adult and fetal cortisol concentrations have been associated with low birth weight (Phillips et al., 2000) and fetal growth restriction (Goland et al., 1993) respectively, and altered HPA axis functioning is associated with depression and anxiety disorders (Van den Bergh, Van Calster, Smits, Van Huffel, & Lagae, 2008).

In relation to PTSD, it is thought by some that HPA axis dysregulation, resulting from fetal growth restriction, leaves an individual at a greater risk of developing PTSD after exposure to a traumatic event (Ronald de Kloet, Oitzl, & Vermetten, 2008; Seckl & Meaney, 2006). However, this hypothesis is based on relationships between PTSD patients and altered stress hormone levels which have recently been challenged as lacking in rigor (Yehuda, 2006) as the directional change and intensity of stress hormone levels in PTSD patients is found to vary in relation to a number of factors involving the stressor and the individual (Miller, Chen, & Zhou, 2007). Despite the lack of clear evidence due to poorly controlled biological research in this area, our study supports the interpretation that lower birth weight or growth restriction may lead to greater vulnerability of developing PTSD. When we restricted our analysis to those exposed to trauma, we found the association between lower birth weight and greater risk of PTSD remained. Importantly, we also found that birth weight did not predict an individual's risk of trauma exposure. Taken together, these findings suggest that lower birth weight does not predict increased risk of experiencing trauma but predicts increased vulnerability to PTSD after a traumatic event is experienced. Our results suggest that, although contentious, the role of HPA axis programming *in utero* as a biological risk factor for PTSD is promising and requires further more rigorous research.

In the absence of a proven biological mechanism, one alternative interpretation needs to be considered. It is possible that residual environmental or shared factors, unable to be captured and controlled in the study, could confound the association we found between low birth weight and the development of adult PTSD in these offspring (Alati et al., 2009). Because diagnosis of PTSD requires exposure to a traumatic event (First and Tasman, 2004), the residual confounding may involve factors which operate before, during or after the traumatic exposure. For example, low birth weight may be associated with residual factors which are themselves associated with increased exposure to early life stress (ELS), which has been found to leave an individual more vulnerable to developing PTSD after subsequent traumas (Heim & Nemeroff, 2001), or decreased social support and additional life stress, which may increase an individual's risk of developing PTSD after exposure to trauma (Brewin, Andrews, & Valentine, 2000). However, if birth weight was associated with such residual factors we may expect to observe these same residual factors predict the risk of exposure to a traumatic event. This was not the case in our study, where the association between birth weight and PTSD was not explained by exposure to trauma.

4.4. Strengths and limitations of the study

The greatest strengths of this study lay in its longitudinal nature which has allowed participants to be followed-up from pre-birth to 21 years. The prospective measurements taken over the 21 year period makes it possible to control for potentially important confounders such as maternal smoking and anxiety during pregnancy and eliminates the potential for recall bias. Another unique strength of this study was that it used the CIDI-Auto to diagnose participants according to DSM-IV criteria, increasing the specificity of the anxiety disorder categories beyond the capacity of other large cohort studies.

The use of a resource intensive diagnostic assessment such as the CIDI-Auto resulted in a larger loss to follow-up then was experienced by other assessments at the 21 year follow-up. While this is the major limitation of the study, it is worth noting that there was no significant difference in our main measure of birth weight between those lost and those retained in the study. This indicates that loss to follow-up was not related to our primary exposure variable and predictor of interest, and does not suggest that attrition has introduced selection bias in our results. In order to further explore this possibility, we created multiply imputed data sets to restore the representation of those lost to follow-up and repeated our analysis.

We found little difference between the imputed and non-imputed results. We are aware of the limitations in all statistical simulations in adequately dealing with attrition bias. However, taken together with these acknowledged limitations, the fact that our main exposure variable was not associated with loss to follow-up and multiple imputation confirmed our results, does indicate some confidence in the robustness of our findings.

Another limitation involved the variables used to adjust for SEP, which has been found to be associated with exposure to trauma (Perkonigg, Kessler, Storz, & Wittchen, 2000). It is worth noting that our SEP measures were taken during a period in which participants were making the transition from dependent to independent living arrangements. Adjustment for socioeconomic position using these indicators may be inadequate to fully account for socioeconomic disadvantage, and it is possible that unmeasured socioeconomic factors could explain associations between birth weight and PTSD.

4.5. Implications and future research

This is the first study to find an association between birth weight and PTSD in adults, and suggests that altered fetal development may be associated with an increased biological risk of developing PTSD after exposure to a traumatic event, but does not place an individual at a greater risk of developing an anxiety disorder unrelated to trauma. While we controlled for the potentially confounding relationship between birth weight and risk of trauma exposure, future epidemiological research into the association should replicate our findings and go further to examine if birth weight is related to other pre- and post-trauma risk factors associated with PTSD and verify possible gender interactions.

Conflict of interest

All authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.janxdis.2011.07.002.

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The association between lower birth weight and comorbid generalised anxiety and major depressive disorder in adult offspring.

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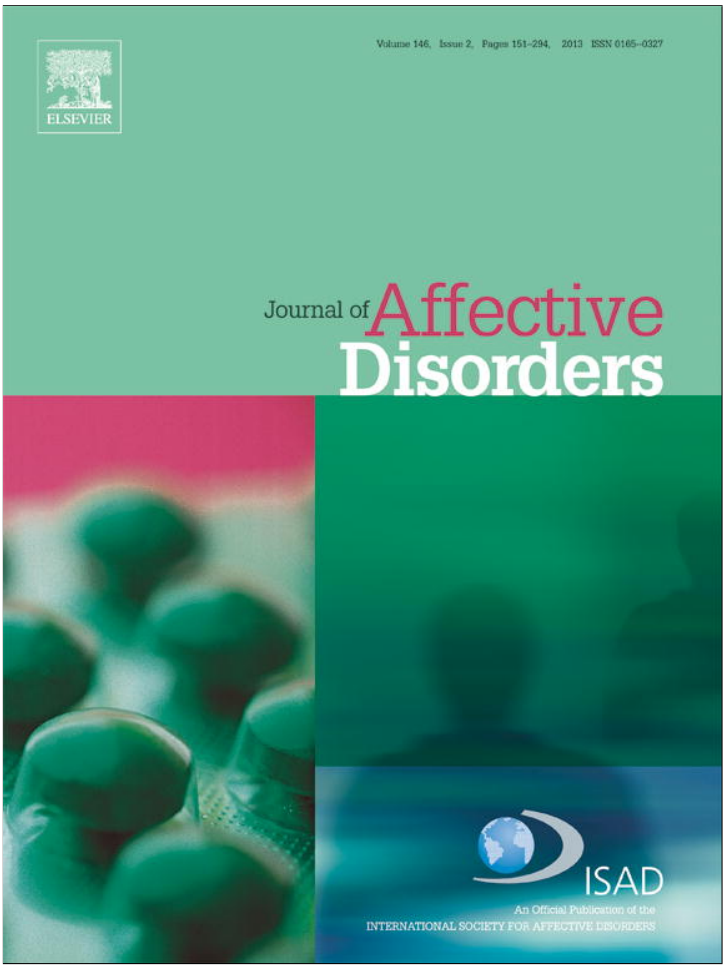
Study purpose: Following the findings of the previous paper which exposed a link between fetal development and more specific anxiety disorders, this study was designed to examine the association between fetal development and two highly comorbid psychiatric disorders (MDD and GAD) while taking this comorbidity into account. Thus as in the previous paper, there was a strong focus on including a more highly specified outcome.

Supplementary material: Some information relevant to this study (i.e., attrition, IPW and MMI analyses) was published online in a supplementary section only and can be accessed at: http://www.sciencedirect.com/science/article/pii/S0165032712006386



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Research report

The association between lower birth weight and comorbid generalised anxiety and major depressive disorder

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ABSTRACT

Objective: Studies testing the association between birth weight and depression or anxiety have found inconsistent results and there has been a lack of research on the possible relationship between birth weight and comorbid anxiety and depression. We tested for an association between lower birth weight and major depression, generalised anxiety and comorbid generalised anxiety and major depression.
Method: Data was taken from 2113 mothers and their offspring participating in the Mater University Study of Pregnancy (MUSP) birth cohort. Generalised anxiety, major depression and comorbid generalised anxiety and major depression at 21 years were tested for associations with birth weight using multinomial logistic regression.
Results: Lower birth weight was found to predict comorbid generalised anxiety and major depression, but did not predict either generalised anxiety or major depression.
Limitations: We were unable to specify comorbidity by the primary disorder, or by the severity or recurrence of the depression.
Conclusion: Previous associations found between birth weight and mental health may reflect a specific link between lower birth weight and comorbid generalised anxiety and major depressive disorders. As neither disorder individually was associated with lower birth weight, this may suggest that this developmental origin represents a unique risk pathway to comorbidity not shared with either discrete disorder.

1. Introduction

The developmental origins of adult disease claim that adaptations made during foetal development in response to a number of maternal and environmental insults result in permanent physiological, neuroendocrine or metabolic changes which may have pathological consequences in later life (Van den Bergh et al., 2005). While this hypothesis has been tested on a wide range of diseases using a variety of indicators of foetal development (Warner and Ozanne, 2010), more recent studies have sought to determine whether foetal growth restriction predicts lasting altered functioning in offspring manifested by increased susceptibility to depression or anxiety. This expanding body of research has so far produced inconsistent results, which can be divided into two main categories and are restricted to studies using samples of adolescents or adults for the purpose of this review. One group of studies used symptoms of psychological or behavioural problems as indicators of mental health problems. Two reports led by this team found an inverse relationship between birth weight and depressive symptoms in 21 year-old females only (Alati et al., 2007), and a non-linear association such that those in the highest and lowest birth weight quintiles were at increased risk of symptoms of anxiety/depression at 14 years of age (Alati et al., 2009). Others have found inverse associations between birth weight and symptoms of distress (Wiles et al., 2005; Cheung et al., 2002) and depressive symptoms (Gale and Martyn, 2004). By contrast further studies reported reduced gestational length but not lower birth weight, predict depressive symptoms (Raikkonen et al., 2007), lower birth weight does not predict depressive symptoms in females (female only sample) (Inskip et al., 2008) and higher birth weight in females predicts depressive symptoms with no association found among males (Herva et al., 2008).

A second group of studies have used categorical diagnostic outcomes. In a previous study from our cohort we found that birth weight was inversely associated with the risk of posttraumatic stress disorders, but not with other DSM-IV anxiety disorders (Betts et al., 2011). In contrast, lower birth weight was associated with any of the anxiety disorders in one study (Nomura et al., 2007) and

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generalised anxiety disorders in another study (Vasiliadis et al., 2010). Regarding lower birth weight and depression, most have found associations with major depression (Nomura et al., 2007) and depressive disorders (Patton et al., 2004; Gudmundsson et al., 2011), while only one study found no evidence for an association (Vasiliadis et al., 2008). There are several explanations for the inconsistencies of these findings. Arguably, some variation would be expected due to considerable methodological differences, which included different age groups, different confounding adjustments and of course different disorders measured in various ways. However, if the birth weight effect later on mental health is real, as found in some studies (Patton et al., 2004; Nomura et al., 2007), and persistent throughout post-childhood development, as the hypothesis suggests, then it is unlikely that these methodological differences could explain null results (Raikkonen et al., 2007; Vasiliadis et al., 2008; Inskip et al., 2008), female specific effects (Alati et al., 2007; Herva et al., 2008), or non-linear (Alati et al., 2009) and positive (Herva et al., 2008) associations.

Another possible explanation of these inconsistent findings may be due to the confounding effect of anxiety on depression or vice versa. It is true that some evidence suggests that both disorders are discrete and separate, having been found to occur independently at a substantial prevalence (Kessler et al., 1999), exhibit unique longitudinal symptom trajectories (Beesdo et al., 2010) and are predicted by separate risk factors (Kessler et al., 2008; Beesdo et al., 2010; Olino et al., 2010; Karevold et al., 2009; Moffitt et al., 2007a; Mathew et al., 2011). However, it has also long been argued that to some degree generalised anxiety and major depression in particular, in aetiological terms, may not be entirely discrete (Mennin et al., 2008). Twin studies consistently show strongly shared heritability between GAD and MDD (Kendler et al., 2007; Kendler, 1996), GAD exhibits higher comorbidity than do other anxiety disorders with major depression and structural equation models show that both disorders load onto the same higher order 'distress disorders' factor (Watson, 2009; Nisita et al., 1990; Vollebergh et al., 2001). In cases where both disorders are expressed in the same person, it had originally been thought that GAD represented a prodrome of MDD, occurring many years earlier (Moffitt et al., 2007b; Nisita et al., 1990). Recent longitudinal studies however have shown that MDD precedes GAD as often as GAD precedes MDD (Moffitt et al., 2007b) and baseline MDD is strongly predictive of subsequent GAD (Kessler et al., 2008). Further, studies have shown that the occurrence of both depression and anxiety is predicted by risk factors which do not predict either discrete disorder (Kessler et al., 2008; Olino et al., 2010). Hence, research thus far does not provide definitive evidence of whether GAD and MDD should be considered as discrete categories and in addition how we should understand comorbidity. Thus, considering the uncertainty surrounding the development of these three conditions, it may be important to investigate risk factors associated with the development of these disorders together.

In this study we examine if there is a differential association between birth weight, and the diagnostic outcomes of generalised anxiety, major depression and comorbid generalised anxiety and major depression, adjusting for important confounders and using data from a prospective birth cohort.

2. Material and methods

2.1. Participants

Participants were from the Mater University Study of Pregnancy (MUSP), a prospective birth cohort started in Brisbane, Australia, between 1981 and 1984. A total of 7223 mothers and offspring (52% male; 48% female) were recruited from the Mater Misericordiae Hospital (MMH) at their first obstetric visit. The MMH accounted for around 50% of all births in Brisbane during the catchment period and resulted in a sample skewed towards lower socio-economic position than the Brisbane average due to the exclusion of private patients attending the MMH. During subsequent follow-ups at the child's birth and of child aged 6 months and 5, 14 and 21 years a range of anthropometric, psychiatric, general health and socioeconomic indicators were collected from both mother and child. Comprehensive details of the MUSP cohort are found elsewhere (Najman et al., 2005). At 21 years 2561 of the offspring completed a psychiatric assessment using the Composite International Diagnostic Interview (CIDI-Auto), of which 2439 had complete data on all variables of interest in the multivariate model. Of these, 326 were not diagnosed with either generalised anxiety or major depression but had been diagnosed with another life time DSM-IV affective or anxiety disorder and were removed from the analyses so that the normative group consisted of participants with no psychiatric diagnoses (full case analysis = 2113). Informed consent from all participants was gained, all data was coded for confidentiality and ethics was approved for the cohort by the institution and funding body.

2.2. Measurement of mood and anxiety disorders

At the 21 year follow-up DSM-IV (First and Tasman, 2004) life time mood and anxiety disorders including generalised anxiety disorders (GAD) and major depression disorders (MDD), along with age at disorder onset and age of most recent experience of symptoms in years, were measured using the CIDI-Auto (World Health Organisation, 1997), which has good validity and inter-rater and test-retest reliability (Peters et al., 1998) and was administered by a trained interviewer. In our sample, 23 of the 114 diagnosed with GAD were diagnosed within the course of another psychiatric disorder. Studies which examined the clinical validity of the GAD hierarchy rule, by which a GAD diagnosis is excluded if it occurred within the course of another selected psychiatric disorder, found that individuals with comorbid GAD + MDD and GAD within MDD have similar increased risks of negative social and functional outcomes compared to MDD only patients (Zimmerman and Chelminski, 2003; Lawrence et al., 2009), and argue that the rule is therefore overly restrictive. Hence, we did not impose the hierarchy exclusion rule for GAD. Importantly, almost all of the comorbid cases in our sample ($n = 62$) had overlapping disorders, meaning they recalled experiencing GAD and MDD simultaneously, though one disorder may have preceded the other originally. Only two people reported recovering from MDD before the onset of GAD, and another two recovered from GAD before the onset of MDD. Due to the close proximity of the occurrence in those with non-overlapping disorders (all within one to four years), the small numbers involved, and the likely importance of cumulative (non-overlapping) comorbidity (Moffitt et al., 2007b), we included these four individuals in the analyses.

2.3. Predictors and confounders

Birth weight, gestational age and gender were extracted from the obstetric records. Of the original 7222 with recorded measures, the average birth weight was 3386 g and the average gestational age at birth was 39.4 weeks. According to clinical cut-offs, 6911 (96%) were born with normal birth weight (≥ 2500 g), 283 (4%) with low birth weight ($2500 < 1499$ g), 25 with very low birth weight ($1500 < 999$ g), and 3 with extremely low birth weight (< 1000 g). As in previous studies (Betts et al.,

2011), foetal growth was estimated by converting birth weight measurements into *z*-scores, internally adjusted for gestational age (weeks) and gender (ranging from −3.21 to+4.14). Possible confounders of the association between birth weight and offspring's mental health include maternal antenatal depression and anxiety during pregnancy, which were measured during pregnancy using the Delusions-States-Symptoms Inventory (DSSI) (Bedford and Folds, 1977). The DSSI depression and anxiety subscales each consists of 7 items which represent the core features of depressive and anxiety disorders, and have been found to correlate well with other established symptoms scales, such as the Edinburgh Postnatal Depression Scale (EPDS) and the Hospital Anxiety/Depression Scale (HADS) (Bedford and Deary 1999). As in previous studies (Alati et al., 2009), binary antenatal depression and anxiety variables were constructed, with women indicating ≥4 symptoms coded as yes. Additional confounders were chosen a priori according to previous epidemiological evidence (Betts et al., 2011; Nomura et al., 2007; Vasiliadis et al., 2008, 2010; Patton et al., 2004; Van den Bergh and Marcoen, 2004; Indredavik et al., 2007; Pawlby et al., 2009), and included maternal smoking (non-smoker, smoker, heavy smoker), alcohol use (abstainer, 0–0.5 drinks/day, >0.05–0.1 drinks/day, >1 drinks/day), age (13–19, 20–34, ≥35) and parity (0, 1–2, ≥3), all were recorded at the time of the mothers first obstetric consultation at the MMH. Concurrent measures of offspring socio-economic position (SEP) were taken at the 21 year follow-up and included offspring income (recoded as low, middle, high) and offspring work type (non-manual, manual, student, other/unemployed).

2.4. Statistical analysis

We used multinomial logistic regression analysis to test for univariate associations between birth weight and confounders with a multinomial outcome including GAD, MDD, comorbid GAD+MDD and participants with no psychiatric morbidity (NPM). In the main analysis, birth weight *z*-score was entered into models as a continuous measure. To address the possibility of a non-linear relationship, birth weight was then entered into the model as a quadratic term. Next, we fitted a final multivariate multinomial regression model adjusting for all confounding variables.

We conducted a series of sensitivity analyses. We replicated the final model using baseline measures of maternal income and education in place of the offspring measures of income and education at 21 years. We also replicated the final model allowing the 326 participants with other psychiatric diagnoses to remain in the normative (N.P.M.) group and controlled for other psychiatric problems (including DSM-IV PTSD, social phobia, panic disorders and dysthymia). This was done due to concerns that by imposing a separate inclusion criteria across different diagnostic groups we may have introduced bias by excluding people with other forms of psychiatric disorder from the N.P.M. group, but not from the other three groups. Finally, multivariate analyses were also replicated using both Social Phobias (SP) and Panic Disorders (PD) separately in place of GAD, to test the ability of birth weight to differentially predict SP+MDD and PD+MDD and their respective discrete forms.

We used two methods to examine how our results may have been affected by loss to follow-up, both with different aims. Firstly, using the participants in the final model (n=2113) we fitted a multivariate logistic regression model to produce weights representing the inverse probability of each participant being included in the study. Variables included in this model were taken at baseline so that these probabilities could be computed with reference to the baseline sample. We then replicated our final analysis using these weights. Secondly, multivariate logistic

Table 1
Univariate multinomial regression showing associations between confounders with three categories of psychiatric outcome including comorbid (GAD+MDD), pure GAD and pure MDD at age 21 [pair-wise comparisons are labelled and expressed as OR with 95% Confidence Intervals (CI)] (complete case analysis n=2, 113).

Confounders	Prevalence% (n)	Comorbid *vs.* N.P.M OR (95% CI)	GAD *vs.* N.P.M OR (95% CI)	MDD *vs.* N.P.M OR (95% CI)
Gender	*Ref*: *Male*			
Female	49.6% (n=1049)	**3.71 (2.08, 6.60)**	**2.67 (1.40, 5.09)**	**2.61 (2.08, 3.27)**
Antenatal alcohol use	*Ref*: *Abstainer*			
>0.5 drinks/day	3.4% (n=73)	0.51 (0.07, 3.81)	1.71 (0.50, 5.84)	1.16 (0.65, 2.08)
0>0.5 drinks/day	49.1% (n=1037)	1.13 (0.68, 1.89)	0.58 (0.30, 1.10)	1.01 (0.81, 1.25)
Maternal age at birth	*Ref*: *35+*			
13–19	13.2% (n=278)	0.83 (0.27, 2.50)	0.97 (0.24, 3.83)	1.45 (0.83, 2.54)
20–34	81.8% (n=1728)	0.56 (0.22, 1.45)	0.66 (0.20, 2.19)	0.98 (0.59, 1.62)
Parity		1.09 (0.89, 1.34)	1.02 (0.79, 1.32)	0.97 (0.88, 1.07)
Offspring education	*Ref*: *Tertiary*			
Secondary incomplete	19.8% (n=418)	1.44 (0.75, 2.77)	1.32 (0.57, 3.03)	**1.73 (1.26, 2.37)**
Secondary complete	55.5% (n=1174)	0.54 (0.29, 1.01)	0.72 (0.35, 1.48)	0.96 (0.73, 1.26)
Offspring income	*Ref: High*			
Low	44.9% (n=948)	1.18 (0.53, 2.63)	1.12 (0.47, 2.64)	1.23 (0.89, 1.69)
Middle	35.9% (n=759)	1.77 (0.84, 3.74)	1.11 (0.48, 2.57)	**1.46 (1.08, 1.99)**
Antenatal anxiety				
Yes	9.6% (n=204)	1.10 (0.47, 2.60)	3.12 (1.50, 6.46)	1.31 (0.92, 1.85)
No	90.4% (n=1909)	1.00	1.00	1.00
Antenatal depression				
Yes	3.5% (n=74)	0.91 (0.22, 3.83)	2.06 (0.62, 6.85)	0.88 (0.48, 1.63)
No	96.5% (n=2039)	1.00	1.00	1.00
Antenatal smoking	Ref: Non-smoker			
Heavy smoker	6.5% (n=137)	1.66 (0.64, 4.31)	3.23 (1.29, 8.11)	**2.01 (1.34, 3.00)**
Smoker	25.5% (n=538)	1.37 (0.77, 2.42)	1.60 (0.81, 3.18)	**1.50 (1.17, 1.91)**

Note: Odds ratios show the unadjusted increased odds of having a psychiatric outcome dependent on the categories of the confounding variables.
N.P.M (no psychiatric morbidity).
Significant odds ratios are shown in bold type.

regression compared the odds of those who were administered the CIDI-Auto at 21 (including the 326 removed from the healthy control group but who had complete data) with those lost to follow-up but with no missing data at baseline by all predictors and confounders (6563 of the original 7223 had values on all baseline variables and were included in this analysis). This was done to observe what factors predicted participants from being unavailable for psychiatric assessment.

3. Results

Of the 2113 participants included in the analyses, 417 (19.7%) were diagnosed with life time MDD, 43 (2.0%) with GAD and 62 (2.9%) with comorbid GAD and MDD. Of the 62 participants with comorbid GAD and MDD, 36 (58.1%) recalled an age of onset (in years) which was the same for each disorder, 17 (27.4%) recalled the onset of MDD prior to GAD and 9 (14.5%) recalled the onset of GAD prior to MDD. The average age at onset for those with MDD only was 16.7 years, for those with GAD only was 16.4 years, and the average age at onset of the primary disorder for those with comorbid GAD and MDD was 16.3 years. Regarding symptomatic recency, among those included in the analyses, 47 of 417 (11%) with MDD only had a current (past month) diagnosis, 14 of 43 (33%) with GAD only had a current diagnosis, and 24 of 62 (39%) with comorbidity had a current diagnosis of at least one of the disorders.

Table 1 shows univariable associations between the confounders and the psychiatric outcomes. The offsprings of mothers who experienced antenatal anxiety were at an increased risk of GAD compared with those with no psychiatric morbidity. Antenatal depression was not found to be associated with any of the outcomes, and antenatal smoking was associated with an increased risk of GAD and MDD when compared to those with no psychiatric morbidity. Females were at an increased risk of all three disorders and lower levels of offspring education and income at 21 years placed individuals at a higher risk of MDD compared to those with no psychiatric morbidity. Table 2 shows the univariable associations between birth weight and the psychiatric disorders, with the outcomes arranged as pair-wise comparisons showing the increased odds of having GAD only, MDD only or comorbid GAD+MDD compared with those with no psychiatric morbidity (N.P.M). Compared to the reference category, there was evidence for an inverse linear association with comorbid GAD+MDD ($p=0.045$), but no association for those with GAD only or MDD only.

Multivariable multinomial analysis (also in Table 2) showed very similar associations between birth weight and the psychiatric outcomes to those found in the univariable analysis. An increase in birth weight *z*-score decreased the odds of being diagnosed with comorbidity compared with N.P.M. (OR 0.81, 95% CI: 0.67, 0.98; $p=0.033$). There was no evidence of a quadratic association between birth weight and the psychiatric outcomes. The results of the two sensitivity analyses, the first which used measures of maternal income and education in place of offspring measures, and the second which did not exclude participants with other psychiatric diagnosis from the N.P.M. group ($n=326$) and adjusted for other DSM-IV disorders, did not differ substantively, with many associations becoming slightly stronger (data not shown but available upon request).

Table 3 shows the results from the multivariable attrition analysis. It is worth noting that birth weight was not differentially associated with loss to follow-up, suggesting that our main exposure was not subject to attrition bias. Both maternal antenatal depression and anxiety were subject to attrition bias, with those lost more likely to have mothers who reported depressive and anxious symptoms during pregnancy. The results from our inverse probability weighting analysis were similar to those

Table 3
Multivariate attrition analysis showing the likelihood of not being lost to follow-up according to baseline factors [expressed as OR with 95% Confidence Intervals (CI) ($n=6563$)].

Effect	OR (95% CI)	*P*-value	*P* for LRT
Birth weight *z*-score	1.02 (0.97, 1.08)	0.358	0.358
Antenatal anxiety	*Reference: no*		
Yes	0.79 (0.66, 0.94)	0.010	0.009
Antenatal depression	*Reference: no*		
Yes	0.66 (0.50, 0.88)	0.004	0.003
Smoking FCV	*Reference: none*		
Smoker	0.94 (0.83, 1.06)	0.288	
Heavy smoker	0.85 (0.69, 1.04)	0.124	0.231
Alcohol FCV	*Reference: none*		
0–0.5 drinks/day	1.19 (1.07, 1.33)	0.001	
0.5–1 drinks/day	0.90 (0.63, 1.27)	0.538	
>1 drinks/day	0.83 (0.52, 1.32)	0.425	0.004
Maternal age at birth	*Reference: ≥35*		
13–19	0.67 (0.49, 0.90)	0.009	
20–34	0.78 (0.60, 1.01)	0.063	0.028
Family income FCV	Reference: $26,000+		
$0–$5199/week	0.51 (0.36, 0.74)	<0.001	
$5200–$15,599	0.76 (0.58, 1.01)	0.054	
$15,600–$25,999	0.80 (0.60, 1.06)	0.116	0.002
Previous births	*Reference: none*		
One or two	0.92 (0.82, 1.04)	0.188	
Three or more	0.74 (0.61, 0.90)	0.033	0.01
Offspring gender	Reference: male		
Female	1.26 (1.14, 1.40)	<0.001	<0.001
Partner status at FCV	*Reference: single*		
Married	0.77 (0.60, 0.99)	0.046	
Living together	1.22 (0.98, 1.53)	0.075	
Separated–widowed–divorced	0.62 (0.40, 0.96)	0.031	<0.001

Table 2
Unadjusted and adjusted multinomial regression showing associations between birth weight *z*-score with three categories of psychiatric outcome including comorbid (GAD+MDD), pure GAD, and pure MDD at age 21 [group comparisons are labelled and expressed as OR with 95% Confidence Intervals (CI)] (complete case analysis $n=2, 113$).

	Unadjusted			**Adjusted**[a]		
Birth weight	Comorbid vs. N.P.M OR (95% CI)	MDD vs. N.P.M OR (95% CI)	GAD vs. N.P.M OR (95% CI)	Comorbid vs. N.P.M OR (95% CI)	MDD vs. N.P.M OR (95% CI)	GAD vs. N.P.M OR (95% CI)
Linear z-score	**0.76 (0.58, 0.99)**	1.15 (0.85, 1.57)	0.96 (0.86, 1.07)	**0.81 (0.67, 0.98)**	1.10 (0.88, 1.37)	0.98 (0.90, 1.04)
P for non-linear	0.062	0.265	0.687	0.076	0.241	0.546

Note: N.P.M (No Psychiatric Morbidity).
Significant odds ratios are shown in bold type.

[a] Adjusted for gender, maternal antenatal depression, anxiety and smoking, and alcohol consumption, parity, mother's age at birth, offspring income and education at 21.

attained in full case analysis (see Supplementary Table 1). Supplementary Tables 2 and 3 show that the birth weight effect was unique to comorbid GAD+MDD, as birth weight did not differentially predict PD+MDD or SP+MDD and their respective discrete disorders compared to those with no psychiatric morbidity.

4. Discussion

This is the first study that has explored associations between birth weight and comorbid generalised anxiety and major depression. By attempting to account for the uncertain but close relationship between anxiety and depression, we aimed to establish a more reliable association between birth weight and later psychopathology. We found that lower birth weight was associated with comorbidity and not with the discrete disorders, highlighting the importance of specifying comorbidity in the outcome. Of note is that our prevalence data matches those of previous studies in which MDD is far more prevalent than GAD, and where the majority of GAD cases are also diagnosed with MDD (Kessler et al., 1999). Importantly, as birth weight did not predict the co-occurrence of panic disorders with major depression or social phobias with major depression and their respective discrete forms compared to those with no psychiatric morbidity, the linear relationship we found between birth weight and GAD+MDD may not simply reflect the more serious nature of the comorbidity of depressive symptoms with anxiety symptoms in general. Earlier studies which have examined the possible role of birth weight in the development of later psychiatric diagnoses have found associations between foetal growth and depressive disorders (Patton et al., 2004; Gudmundsson et al., 2011), MDD and anxiety disorders (Nomura et al., 2007), GAD (Vasiliadis et al., 2010) and post-traumatic stress disorders (Betts et al., 2011), but no study to date has tested for specific comorbid outcomes. In light of our findings, it is possible that past studies may have found more robust relationships had they specified the outcome to include comorbid depression and anxiety.

We propose that our findings may result from a biological process linking birth weight with comorbid generalised anxiety and major depression. This proposition is supported by evidence showing that offspring increased cortisol levels are associated with low birth weight (Phillips et al., 2000) and foetal growth restriction (Goland et al., 1993), and that increased hypothalamic–pituitary–adrenal (HPA) functioning is associated with depressive disorders (Van den Bergh et al., 2008; Vreeburg et al., 2009). Further, recent biological studies have found that the increased HPA functioning associated with MDD patients compared with controls is due to (Young et al., 2004), or is higher (Vreeburg et al., 2009) among those with co-occurring anxiety disorders. However, as the biological studies employed non-specific groups of anxiety disorders, we may also expect to have found an association between birth weight and the other anxiety disorders comorbid with MDD. Instead we found a relationship which was specific to the combination of symptoms from major depression and generalised anxiety. Importantly, we must give consideration to an alternative explanation for our results. It is possible that the relationship between birth weight and adult psychiatric outcomes are both fully or partly the result of unmeasured environmental, social and familial factors. However, as the point estimates remained unchanged after adjustment for a wide range of maternal and social factors, this may suggest that residual environmental or familial confounding is unlikely to explain the results.

Our findings are also of importance to another line of research which aims to determine what unique risk factors predict comorbid depression and anxiety in efforts to reduce the prevalence of this condition, shown to be more debilitating than either discrete disorder (Mathew et al., 2011). Taken together, this literature provides four main points relative to the relationship between anxiety, depression and comorbidity. Firstly, there is evidence of shared risk pathways to anxiety and depression (Karevold et al., 2009). Secondly, anxiety and comorbidity have more shared risk factors than do depression and comorbidity (Karevold et al., 2009; Moffitt et al., 2007a). Thirdly, primary anxiety is predictive of subsequent major depression (Mathew et al., 2011), and primary depression is predictive of subsequent anxiety (Kessler et al., 2008). Finally, all studies also found evidence that anxiety and depression were predicted by unique risk factors (Kessler et al., 2008; Beesdo et al., 2010; Olino et al., 2010; Karevold et al., 2009; Moffitt et al., 2007a; Mathew et al., 2011), and that comorbidity has risk factors that are unique when compared with both discrete generalised anxiety and major depression (Kessler et al., 2008; Olino et al., 2010). These studies had important limitations. Half of the studies resembled descriptive analyses, by which outcomes were associated with social, behavioural or lifestyle correlates (Kessler et al., 2008; Beesdo et al., 2010; Olino et al., 2010). Of the three studies which specified a theoretical model, one simply tested bivariate associations (Moffitt et al., 2007a), another used all anxiety disorders instead of generalised anxiety (Mathew et al., 2011), and the other did not use DSM diagnoses (Karevold et al., 2009). In addition, three studies used the DSM-III generalised anxiety diagnosis (Moffitt et al., 2007a; Mathew et al., 2011; Kessler et al., 2008) which differs importantly from the DSM-IV diagnosis (Mennin et al., 2008). Our findings provide a unique contribution to this line of research, building on earlier studies which sought to establish a relationship between foetal development and later psychiatric outcomes, our results may indicate a biological process which is both strongly predictive of DSM-IV comorbid generalised anxiety and major depression.

Importantly, our data has some limitations. Our specification of comorbidity consisted of a single grouping, while recent studies have shown the importance of specifying comorbidity by primary disorder (Kessler et al., 2008; Mathew et al., 2011). Ideally, a larger sample and multiple prospective follow-ups would have allowed investigation of associations with multiple and unique comorbid groupings. Further, the small numbers of GAD cases prevented us from operationalising a comorbid variable which specified depressive severity and recurrence. Likewise, small numbers, retrospective recall of onset and the fact that the majority of individuals with life time comorbid GAD+MDD recalled the same age at onset for both disorders prohibited us from classifying comorbidity by the primary disorder. As such, it remains possible that rather than predicting comorbidity, birth weight predicts a level of anxiety severity which increases the chances of later depression or vice versa. Another limitation of our data was the considerable loss to follow-up, which we addressed in two ways. Firstly, the multivariate attrition analysis revealed that birth weight was not associated with loss to follow-up, giving some confidence that our results may not be subject to attrition bias. Secondly, results from our inverse probability weighting analysis were similar to our full case analysis.

In conclusion, we found for the first time that birth weight was uniquely associated with the specific combination of comorbid generalised anxiety and major depression in a sample of young adults. This may reveal a specific link between birth weight and comorbid generalised anxiety and major depressive disorders which earlier studies using discrete disorders did not test. Considering our findings and the continued controversy surrounding the classification of depression and generalised anxiety, we suggest research into the risk factors of depression and generalised anxiety could be benefited by incorporating both disorders and comorbidity into the outcome. In addition, we have discovered that processes

affecting the outcome of foetal development may form a unique risk pathway to the development of a debilitating and common psychiatric comorbidity. Future studies must be carried out to elucidate these processes and identify related processes in early childhood to inform interventions and thus reduce the burden of adult psychiatric disorders which a growing body of evidence is attributing to early development.

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Conflict of interest

All authors declare no conflicts of interest exist.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jad.2012.09.010.

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Chapter 5 - Intergenerational transference of psychopathology from mother to child

The association between maternal depressive, anxious and stress symptoms during pregnancy predict internalising problems in adolescence

Published manuscript and formal citation

Betts, K. S., Williams, G. M., Najman, J. M. & Alati, R. (2014). Maternal depressive, anxious, and stress symptoms during pregnancy predict internalizing problems in adolescence. *Depression and Anxiety* 31, 9-18.

Study purpose: This paper was designed to extend research into the relationship between maternal prenatal psychopathology and offspring psychopathology at later stages of development (adolescence), in addition to improving the methodological design for controlling for ongoing maternal psychopathology after pregnancy.

Supplementary material: Some information relevant to this study (i.e., attrition, IPW and MMI analyses) was published online in a supplementary section only and can be accessed at: http://onlinelibrary.wiley.com/doi/10.1002/da.22210/suppinfo

Research Article

MATERNAL DEPRESSIVE, ANXIOUS, AND STRESS SYMPTOMS DURING PREGNANCY PREDICT INTERNALIZING PROBLEMS IN ADOLESCENCE

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Background: *Studies have shown a link between maternal–prenatal mental health and offspring behavior problems. In this paper, we derived longitudinal trajectories of maternal depressive, anxious, and stress symptoms over early life to predict offspring behavior in adolescence.* **Methods:** *Participants included 3,925 mother–offspring pairs from the Mater University Study of Pregnancy (MUSP), an Australian-based, prebirth cohort study. Latent class growth analysis with parallel processes was used to identify trajectories of maternal depressive, anxious, and stress symptoms over four measurement periods between the mothers' first clinic visit and 5 years postpregnancy. The estimates from the maternal trajectories were used to fit multivariate logistic regression models and predict internalizing and externalizing behavior at age 14. We adjusted for a wide range of factors, including a number of prenatal confounders, concurrent maternal depressive and anxious symptoms, father's history of mental problems, and maternal life events relationship quality and contact with the new born.* **Results:** *Seven maternal trajectories were identified one of which isolated high levels of depressive, anxious, and stress symptoms during pregnancy. After adjustment for confounders, this was the only trajectory that predicted higher internalizing behavior in adolescence. No specific maternal trajectory predicted externalizing problems.* **Conclusions:** *We found evidence for a prenatal effect, whereby high levels of maternal depression, anxiety, and stress symptoms in early pregnancy uniquely increased the risk of internalizing behavior problems in adolescence. Depression and Anxiety 0:1–10, 2013.*

Key words: *prenatal depression; anxiety and stress; latent class growth analysis; internalizing; externalizing; adolescence*

INTRODUCTION

Fetal growth is a sensitive period in which maternal and environmental insults, including not only maternal malnutrition but depression and anxiety, can alter fetal development having a lasting impact on the offspring's neurological and behavioral development.[1–3] Confidence that the observed relationship between

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prenatal depression and anxiety with offspring behavior is underpinned by genuine biological mechanisms comes from experiments in animal models.[4,5] Recently, human studies with good capacity to account for individual and environmental factors, such as genetic continuity and postnatal mental health problems also, point to a prenatal effect.[6–8] In addition, other evidence shows that maternal stress experienced during the prenatal period may be more strongly related to offspring psychopathology than prenatal depression or anxiety.[9,10] Though highly correlated with mental health symptoms, self-perceived stress symptoms are considered separate to depressive and anxious symptoms,[3] and are often conceptualized as a manifestation of the subjective physical and mental toll exacted from the mother in response to a broad range of daily hassles and life events.[9,11,12]

The impact of prenatal depression, anxiety, or stress upon outcomes among adolescents is not well established, since most evidence that originates from broad scale, birth cohort data compose of samples of preadolescent children.[3,13–17] These studies have considerable weaknesses. First, the majority have relied on maternal reports of offspring behavior,[3] which are likely to be biased by mother's own mental health problems.[18] Another important weakness of the existing literature is the possibility of residual confounding that remains one of the greatest concerns to internal validity in this field of research. Mothers experiencing prenatal depression or anxiety are more likely to be depressed and anxious in the months and years following pregnancy,[19] and parental modeling of depressive and anxious behaviors may increase the child's learned helplessness and threat perception.[20] Additionally, postnatal maternal mental health problems are found to associate with parenting more withdrawn and disinterested in quality.[21] Hence, it is possible that life course exposure rather than prenatal exposure to maternal depression, anxiety, or stress accounts for the increase in child behavior problems. This is supported by studies where associations between maternal prenatal anxiety and stress with child behavior or emotional problems weakened substantively after adjustment for maternal postnatal anxiety and depression.[12,14,15] Alternatively, both maternal postnatal mental health problems and negative offspring development may be caused by shared individual and environmental factors, such as parental relationship quality and stressful life events.[22–24] Lastly, most studies have not accounted for the role of the father's mental health, thereby ignoring his known contribution to offspring mental health via modeling, parenting, or genetic inheritance.[7]

Studies into maternal prenatal and postnatal mental health have focused mainly on symptoms of depression with fewer investigations into anxiety and fewer yet into subjective stress.[25,26] Focusing on a single psychological construct ignores the empirical and theoretical overlap between these measures, serving to overemphasize whichever construct is tested in isolation.[25] Such focus also underestimates statistical associations with outcomes, as the undue focus on a single construct fails to specify the smaller group who exhibit psychological disturbance across multiple constructs in addition to the increasingly severe symptoms known to occur in those with comorbid conditions.[25,26]

In this study, we investigate symptoms of all three constructs simultaneously, by identifying empirical trajectories of maternal depressive, anxious, and stress symptoms from pregnancy to child age 5 and use these to predict offspring behavior problems. By isolating the various levels of these symptoms as they are found to naturally exhibit in mothers at either single or multiple time points, this unique explorative methodology will provide a valuable perspective regarding at what time and which symptoms are most critical to predicting behavior problems. We also add to the existing evidence by using offspring self-reported behavior problems in adolescence, and adjusting for father's history of mental problems, and postnatal factors, such as maternal relationship quality, life events, and infant rearing.[22–24]

METHODS

PARTICIPANTS

Participants came from the Mater University Study of Pregnancy (MUSP), a prospective prebirth cohort study following mothers and their children for over 20 years. Seven thousand two hundred twenty-three mothers attending their first clinic visit (FCV) at Brisbane's Mater Misericordiae Hospital were recruited between 1981 and 1984, with subsequent follow-ups at birth, and child age 6 months, and 5, 14, and 21 years. The resulting sample of women, restricted to public patients, was skewed toward lower sociodemographic backgrounds (age, education, and income), and were more likely to smoke and be unmarried during pregnancy than the Brisbane average.[27] Although 4,891 mothers with complete data formed the sample for the trajectories analysis, the regression analyses were restricted to the 3,925 mother–offspring pairs with complete values on all variables of interest.

MEASUREMENT OF MATERNAL DEPRESSIVE, ANXIOUS, AND STRESS SYMPTOMS

All three measures were collected at the four time points of FCV (i.e., the prenatal measure), 3–5 days after birth and at child 6 months and 5 years of age. Depressive and anxious symptoms were measured using the Delusions-States-Symptoms Inventory (DSSI) that includes subscales, both consisting of seven items designed to include the primary features of anxiety and depression.[28] The DSSI has been found to correlate well with other established symptoms scales including the Edinburgh Postnatal Depression Scales (EPDS) and the Hospital Anxiety/Depression Scale (HADS).[29] Stress symptoms were measured using the four-item Reeder stress inventory (RSI), designed to measure self-perceived daily strain resulting from the physiological and psychological reactions to personal or social situations, such as daily hassles, major events, and coping resources.[11,30] A recent validation study has supported the construct validity of the RSI.[31] To define cases for anxiety, depression, and stress, the frequency of experiencing the symptoms from 1 (never) to 5 (always) was summed separately across each construct (for the $n = 4,891$ mothers), with each construct then dichotomized with the 10% of individuals with the highest scores representing cases.

MEASUREMENT OF ADOLESCENT BEHAVIORS

At the 14-year follow-up, adolescents completed the Achenbach youth self-report (YSR).[32] The YSR includes internalizing and externalizing behavior problems that are summary measures of a number of subscales: internalizing (anxiety/depression, somatic, and withdrawn subscales); externalizing (aggression and delinquency subscales). To each question, respondents answer on a 3-point scale including often/sometimes/rarely or never, and the scores within each summary measure are then summed with the top 10% representing clinically significant behavior problems.[32,33] The validity and internal consistency of the YSR scales within the MUSP have been reported in previous studies.[34]

CONFOUNDING VARIABLES

We adjusted for a number of a priori covariables that may confound the relationship between maternal prenatal depression, anxiety, and stress with offspring outcomes.[17] Birth weight, gestational age (GA), gender, and parity were taken from obstetric records at the time of birth. We used a continuous measure of birth weight *z*-scores internally adjusted for GA and gender as an indicator of fetal growth.[35–37] At FCV and birth, mothers' maternal smoking (nonsmoker/light to moderate/heavy smoker) and alcohol consumption (abstainer/light drinker/moderate drinker/heavy drinker) were used. Maternal education (tertiary studies/high school completed/high school uncompleted) was included as an indicator of socioeconomic position and was recorded at FCV along with maternal age in years. At the 5- and 14-year follow-up, mothers were asked if their partner had seen a doctor because of a mental or emotional problem (no problem/problem by child 5 years/problem after child 5 years). Finally, we adjusted for maternal depression and anxiety concurrent to the adolescent behavior outcomes using the DSSI measured at 14 years (there were no available measures of stress at the 14-year follow-up).

We also adjusted for a number of factors ascertained 3–5 days after birth, which studies show may be related to postnatal mental health and offspring behavioral development.[22–24] A shortened version of the Life Events Scale[38] was completed, which composed of eight possible negative events asked in relation to the prior 6 months, and the resulting variable was dichotomized by the number of events (0–3/4 or more). Conflict between the mother and her intimate partner was assessed using the Spanier Dyadic Adjustment Scale.[39] Maternal contact with newborn was measured with a five-item index exploring the attitude of the mother toward her new born: relieved when baby taken to nursery, prefer not to have the baby at night, cannot resist nursing the baby, love to play with the baby, wish I could have the baby all the time (strongly agree/agree/neutral/disagree/strongly disagree). Because the majority of respondents indicated high levels of contact with baby and low levels of conflict with partner, both variables were categorized immediately after measurement with the two higher categories of each variable representing the extreme ends of the distribution.[40]

STATISTICAL ANALYSES

We used a three process parallel latent class growth analysis (LCGA) to derive trajectories of maternal depressive, anxious, and stress symptoms from FCV to 5 years (n = 4,891) using Mplus version 6.[41] We compared a number of LCGA models, from 2 to 8 classes, including constant, linear, and quadratic growth functions. Although our model simultaneously included depressive, anxious, and stress symptoms, the three constructs were "free" to express separately or in combination across time. We used the Bayesian information criterion (BIC) and Lo-Mendell-Rubin adjusted Likelihood Ratio Test (LMRT) as the principal indices of best fit and the bootstrap likelihood ratio test (BLRT) to ensure the "best" model provided a significantly improved fit compared with the k – 1 class model,[42] but were also guided by theoretical considerations (i.e., identification of a prenatal trajectory without overfitting). The class probabilities (trajectories) were then exported to Stata version 11 for regression analyses. This is a common approach in the LCGA literature,[43] and a satisfactory approach with an entropy $\geq$0.80.[44]

We then tested the univariate associations first, between the confounders and the trajectories, and second, between the confounders with behavior at 14. Next, univariate and multivariate, logistic and linear regressions were used to test the associations between the different maternal trajectories and the YSR behavior outcomes, adjusted for confounders. We compared those who had been lost to follow-up with those who were retained in the regression analyses on a number of baseline variables to explore predictors of attrition. Next, we undertook multivariate imputations analysis using the Imputations by Chained Equations (ICE) procedure in Stata. Starting from a missing at random assumption,[45] we used 20 cycles of regression to generate 20 imputed datasets for the original sample of 7,223 mother–offspring pairs. We then replicated our final analysis using the imputed data.

RESULTS

The tetrachoric correlations among maternal depressive, anxious, and stress symptoms reveal strong relationships between contiguous time points within the same constructs, and strong relationships between different constructs at the same time point (Table 1). A model with seven trajectories and quadratic growth factors (BLRT < 0.001) was regarded as the best solution (Fig. 1). Although the BLRT and BIC indicated a better fit for an eight class solution, the LMRT indicated overfitting and the prenatal trajectory was no different from the seven class solution (Supporting Information Table S1). The seven trajectories included (1) depressive, anxious, and stress symptoms during pregnancy (i.e., the prenatal group), (2) during birth, (3) at 6 months, and (4) at 5 years; in addition, (5) ongoing depressive, anxious, and stress over the entire period, (6) ongoing stress symptoms (only) over the entire period, and (7) a normative group (not shown).

Maternal smoking at FCV and birth, mother's life events and intimate relationship at birth, and concurrent maternal symptoms of anxiety and depression at child age 14 were strongly predictive of some trajectories (see Table 2). Gender, maternal alcohol use, and birth weight did not predict any trajectories. Table 3 shows univariate associations between confounding variables and adolescent reported behavior at age 14. Females were more likely to experience internalizing, whereas males were at greater odds for externalizing, and a number of other covariables were found to predict adolescent internalizing and externalizing behavior.

Table 4 shows univariate and multivariate associations between maternal trajectories and internalizing and externalizing behavior at 14. After adjustment for all covariates, logistic regression found one significant relationship between prenatal depressive, anxious, and stress symptoms with internalizing behavior. In attenuating associations to the null, the strongest covariables were maternal smoking at FCV and at birth (model 1) and

TABLE 1. Correlations among the different groups of maternal symptoms at each time point (n = 4,891)

Symptoms	Prev (%)	Anx 1	Anx 2	Anx 3	Anx 4	Dep 1	Dep 2	Dep 3	Dep 4	Stress 1	Stress 2	Stress 3	Stress 4
Anx 1	434 (8.9)	1.00	**0.03**	**0.03**	**0.03**	**0.02**	0.03	0.03	0.03	**0.03**	0.03	0.03	0.04
Anx 2	568 (11.6)	**0.60**	1.00	**0.03**	**0.03**	0.03	**0.02**	0.03	0.03	0.02	**0.02**	0.03	0.03
Anx 3	500 (10.2)	**0.55**	**0.58**	1.00	**0.03**	0.03	0.03	**0.01**	0.03	0.03	0.03	**0.02**	0.03
Anx 4	455 (9.3)	**0.48**	**0.52**	**0.56**	1.00	0.03	0.03	0.03	**0.02**	0.03	0.04	0.03	**0.02**
Dep 1	566 (11.6)	**0.80**	0.54	0.51	0.39	1.00	**0.02**	**0.03**	**0.03**	**0.03**	0.03	0.03	0.03
Dep 2	442 (9.0)	0.58	**0.84**	0.55	0.42	**0.64**	1.00	**0.03**	**0.03**	0.03	**0.03**	0.03	0.04
Dep 3	502 (10.3)	0.51	0.50	**0.86**	0.45	**0.60**	**0.62**	1.00	**0.03**	0.03	0.03	**0.02**	0.03
Dep 4	540 (11.0)	0.41	0.41	0.47	**0.83**	**0.40**	**0.42**	**0.48**	1.00	0.04	0.03	0.03	**0.03**
Stress 1	449 (9.9)	**0.62**	0.45	0.48	0.36	**0.60**	0.50	0.48	0.31	1.00	**0.03**	**0.03**	**0.03**
Stress 2	399 (8.2)	0.47	**0.67**	0.51	0.41	0.50	**0.66**	0.51	0.38	**0.65**	1.00	**0.02**	**0.03**
Stress 3	482 (9.9)	0.43	0.44	**0.71**	0.42	0.42	0.44	**0.68**	0.38	**0.63**	**0.67**	1.00	**0.03**
Stress 4	465 (9.5)	0.37	0.36	0.47	**0.70**	0.32	0.30	0.38	**0.60**	**0.48**	**0.54**	**0.56**	1.00

Time 1, first clinic visit (prenatal); Time 2, at birth; Time 3, 6 months after birth; Time 4, 5 years after birth. Anx, anxiety; Dep, depression.
Sample tetrachoric correlations are in the lower triangle. Standard errors (*SE*) of the correlations are in the upper triangle.
Correlations within the same symptom group bolded and underlined; correlations between different symptoms groups at the same time point bolded.
Significance was calculated as the ratio of the correlation divided by the *SE* compared to the critical value of 1.96 ($P < 0.05$ (two-tailed) for all coefficients shown)

relationship quality (model 2). Linear regression analyses, which used continuous measures of the internalizing and externalizing scores, supported results from the logistic regression, and this increase in internalizing score for offspring exposed to prenatal depressive, anxious, and stress symptoms was significantly greater when compared with all other trajectories except ongoing stress only (depression, anxiety, and stress at birth

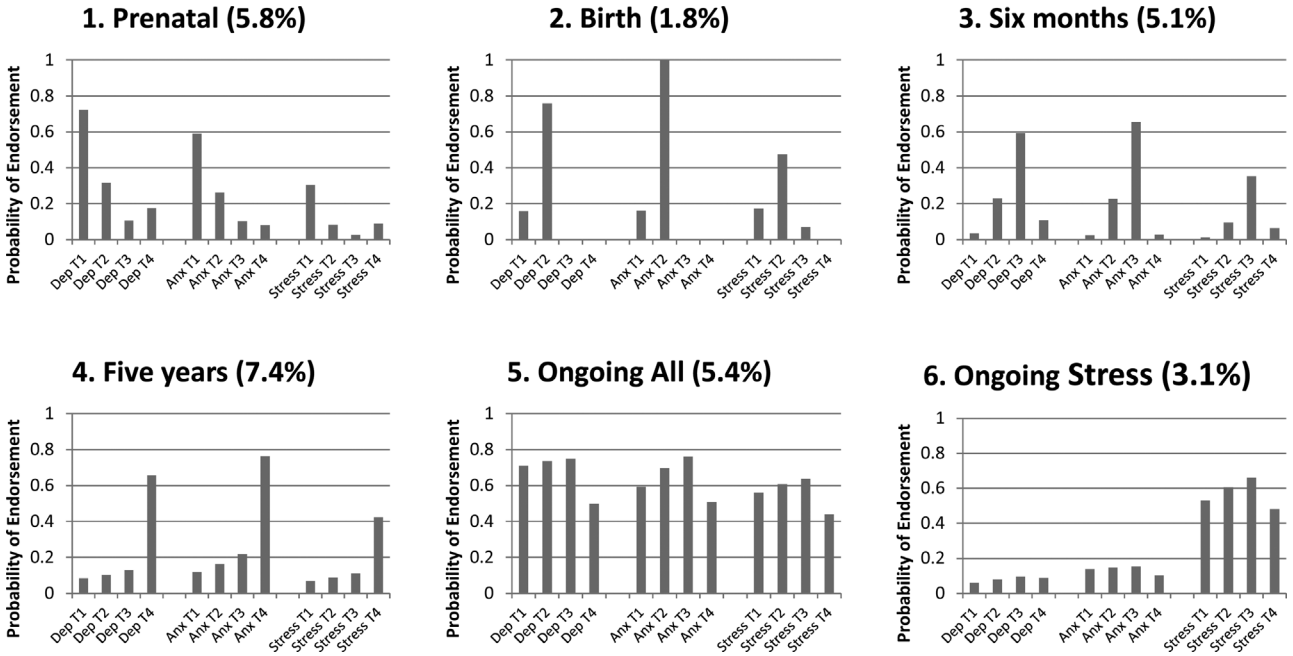

Figure 1. Seven class latent class growth analysis (LCGA) solution showing the probability of each of the six nonnormative classes of endorsing depression (Dep), anxiety (Anx), and stress (Stress) at each time point—pregnancy (T1), birth (T2), child 6 months (T3), child 5 years (T4).
Note: Classes are labeled depending on the time point/s at which they exhibit the strongest probability of endorsement with the percentage of the sample in each class shown in parenthesis (the normative class is not shown).
Model fit indices: BIC = 30,340; entropy = 0.88; bootstrap likelihood ratio test BLRT < 0.001 (Supporting Information Table S3 contains comprehensive fit indices for all tested models).

TABLE 2. Multinomial logistic regression of the univariate associations between maternal trajectories of depression, anxiety, and stress, and stress only with confounding variables (expressed as OR with 95% confidence intervals [CI]; $n = 3,925$)

Confounders	Prevalence *n* (%)	Discontinuous Dep/Anx/Stress trajectories				Ongoing Dep/Anx/Stress trajectories	
		Prenatal OR (95% CI)	Birth OR (95% CI)	6 Months OR (95% CI)	5 Years OR (95% CI)	Distress OR (95% CI)	Stress only OR (95% CI)
Gender							
Male	2,035 (51.8)	1.00	1.00	1.00	1.00	1.00	1.00
Female	1,890 (48.1)	0.95 (0.70, 1.29)	1.40 (0.87, 2.25)	1.09 (0.81, 1.46)	1.03 (0.80, 1.32)	0.81 (0.60, 1.10)	1.37 (0.94, 2.00)
Mat smoke preg.							
None	2,657 (67.7)	1.00	1.00	1.00	1.00	1.00	1.00
Light/moderate	1,024 (26.1)	2.12 (1.53, 2.93)	1.48 (0.89, 2.47)	1.23 (0.88, 1.73)	1.52 (1.16, 2.01)	1.68 (1.19, 2.37)	1.20 (0.78, 1.84)
Heavy	244 (6.2)	3.32 (2.01, 5.50)	0.97 (0.30, 3.16)	2.06 (1.21, 3.52)	2.16 (1.36, 3.42)	4.60 (2.95, 7.17)	1.36 (0.62, 3.00)
Mat alc preg.	3,925 (100)	1.16 (0.91, 1.49)	0.87 (0.58, 1.31)	1.07 (0.84, 1.37)	1.01 (0.81, 1.24)	1.23 (0.97, 1.57)	1.03 (0.75, 1.41)
Mat smoke birth							
None	2,609 (66.5)	1.00	1.00	1.00	1.00	1.00	1.00
Light/moderate	940 (24.0)	2.03 (1.46, 2.84)	1.73 (1.04, 2.87)	1.26 (0.89, 1.80)	1.66 (1.25, 2.19)	1.35 (0.93, 1.97)	1.16 (0.74, 1.80)
Heavy	376 (9.6)	2.45 (1.55, 3.87)	0.82 (0.29, 2.29)	2.25 (1.46, 3.46)	1.68 (1.11, 2.53)	4.20 (2.87, 6.14)	1.17 (0.60, 2.29)
Mat alc birth	3,925 (100)	1.15 (0.92, 1.430	0.86 (0.58, 1.29)	1.16 (0.93, 1.44)	0.98 (0.81, 1.20)	1.01 (0.80, 1.28)	1.11 (0.83, 1.47)
Zbwt	3,925 (100)	0.97 (0.87, 1.08)	1.10 (0.93, 1.30)	1.00 (0.90, 1.11)	0.99 (0.91, 1.08)	0.95 (0.85, 1.06)	1.13 (0.98, 1.29)
Mothers' age	3,925 (100)	0.92 (0.88, 0.95)	1.00 (0.95, 1.05)	0.99 (0.96, 1.02)	0.97 (0.94, 0.99)	1.01 (0.98, 1.04)	1.04 (1.01, 1.08)
Parity	3,925 (100)	0.80 (0.68, 0.93)	1.19 (0.99, 1.43)	1.06 (0.94, 1.21)	1.03 (0.93, 1.15)	1.26 (1.12, 1.41)	1.31 (1.41, 1.51)
Mother's education							
Tertiary	774 (19.7)	1.00	1.00	1.00	1.00	1.00	1.00
High school	2,535 (64.6)	1.18 (0.79, 1.79)	1.28 (0.65, 2.49)	1.67 (1.08, 2.59)	1.42 (1.01, 2.02)	1.13 (0.74, 1.71)	0.64 (0.42, 0.98)
Incomp. high school	616 (15.7)	1.54 (0.93, 2.55)	2.04 (0.94, 4.45)	1.80 (1.05, 3.08)	1.61 (1.04, 2.49)	2.06 (1.28, 3.33)	0.60 (0.32, 1.13)
Newborn contact							
Wanted	3,326 (84.7)	1.00	1.00	1.00	1.00	1.00	1.00
Borderline	285 (7.3)	1.37 (0.80, 2.34)	1.52 (0.69, 3.38)	1.72 (1.04, 2.83)	1.00 (0.61, 1.66)	1.52 (0.89, 2.60)	1.88 (1.01, 3.50)
Not wanted	314 (8.0)	1.20 (0.68, 2.11)	1.09 (0.43, 2.74)	2.44 (1.58, 3.77)	1.28 (0.82, 2.02)	2.76 (1.80, 4.22)	2.97 (1.77, 5.00)
Mother life events							
0–3	3,732 (95.1)	1.00	1.00	1.00	1.00	1.00	1.00
4 or more	193 (4.9)	3.21 (1.87, 5.51)	2.84 (1.20, 6.72)	3.26 (1.92, 5.52)	2.19 (1.30, 3.69)	7.16 (4.67, 11.00)	2.34 (1.11, 4.95)
Intimate partner							
Good	3,473 (91.0)	1.00	1.00	1.00	1.00	1.00	1.00
Moderate	309 (7.9)	3.00 (1.91, 4.73)	3.28 (1.69, 6.37)	1.83 (1.08, 3.10)	3.06 (2.10, 4.46)	7.34 (5.06, 10.67)	2.80 (1.59, 4.94)
Conflict	43 (1.1)	10.01(3.69,27.65)	-	7.55 (2.60, 22.00)	4.40 (1.39, 13.92)	32.19(14.44,71.46)	5.22 (1.14, 23.88)
Anxiety at 14							
No	3,520 (89.7)	1.00	1.00	1.00	1.00	1.00	1.00
Yes	405 (10.3%)	2.97 (2.08, 4.22)	2.06 (1.14, 3.74)	4.33 (3.13, 5.99)	6.77 (5.19, 8.84)	10.26(7.47,14.08)	2.77 (1.78, 4.31)
Depression at 14							
No	3,636 (92.6)	1.00	1.00	1.00	1.00	1.00	1.00
Yes	289 (7.4)	3.11 (1.88, 5.13)	1.48 (0.53, 4.14)	8.49 (6.09, 11.83)	1.64 (0.75, 3.61)	11.52(8.00,16.61)	1.64 (0.75, 3.61)
Father mental prob.							
Never	3,547 (90.4)	1.00	1.00	1.00	1.00	1.00	1.00
Before 5 years	176 (4.5)	1.25 (0.50, 2.61)	0.38 (0.05, 2.75)	1.16 (0.56, 2.42)	2.50 (1.56, 4.00)	3.42 (2.07, 5.68)	2.30 (1.13, 4.67)
After 5 years	202 (5.1)	1.43 (0.78, 2.64)	1.16 (0.42, 3.22)	0.89 (0.43, 1.84)	1.50 (0.90, 2.49)	1.83 (1.03, 3.25)	1.17 (0.50, 2.71)

Note: There were too few cases of maternal intimate partner conflict in those in the 6-month distress trajectory to calculate a sensible effect size.
As a four-level categorical variable, prenatal alcohol use could not be used in a multinomial regression with a seven categorical outcome variable due to small and missing numbers in cells. Thus, it was entered as a continuous variable for descriptive purposes in this analysis only.
The prevalence of alcohol use at each time point was first clinic visit (none = 48.2%, light = 48.4%, moderate = 1.4%, high = 1.0%) and at birth (none = 62.4%, light = 32.9%, moderate = 3.0%, high = 1.7%); Zbwt (continuous *z*-score of birth weight internally adjusted for gestational age and gender).

TABLE 3. Logistic regression showing associations between adolescent-reported internalizing and externalizing behavior problems at 14 with confounding variables (expressed as OR with 95% confidence intervals [CI]; $n = 3{,}990$)

YSR scales (10%)	Internalizing OR (95% CI)	Externalizing OR (95% CI)
Covariables		
Gender	Ref: male	
Female	2.00 (1.61, 2.49)	0.76 (0.61, 0.95)
Mat smoke preg.	Ref: none	
Light/moderate	1.35 (1.07, 1.70)	1.68 (1.32, 2.14)
High	1.68 (1.14, 2.47)	2.07 (1.40, 3.06)
Mat alc. Preg.	Ref: none	
Light	1.14 (0.92, 1.42)	1.05 (0.84, 1.31)
Moderate	1.44 (0.77, 2.70)	0.59 (0.24, 1.48)
High	0.80 (0.24, 2.62)	1.51 (0.58, 3.89)
Mat smoke birth	Ref: none	
Light/moderate	1.33 (1.04, 1.70)	1.85 (1.45, 2.37)
High	1.85 (1.35, 2.54)	2.11 (1.51, 2.93)
Mat alc. Birth	Ref: none	
Light	0.99 (0.79, 1.24)	0.95 (0.75, 1.21)
Moderate	0.74 (0.37, 1.48)	1.15 (0.62, 2.12)
High	1.61 (0.81, 3.19)	1.60 (0.78, 3.28)
Zbwt	0.93 (0.84, 1.04)	0.97 (0.86, 108)
Mothers' age	0.99 (0.97, 1.01)	0.96 (0.94, 0.99)
Parity	1.10 (1.01, 1.20)	1.08 (0.99, 1.19)
Mother's education	Ref: tertiary	
High school	1.24 (0.93, 1.64)	1.70 (1.22, 2.36)
Incomp. high school	1.24 (0.86, 1.79)	2.02 (1.36, 3.01)
Newborn contact	Ref: wanted	
Borderline	1.15 (0.78, 1.71)	1.17 (0.78, 1.76)
Not wanted	1.26 (0.88, 1.81)	1.35 (0.93, 1.96)
Mother life events	Ref: 0–3	
4 or more	1.90 (1.28, 2.81)	1.50 (0.97, 2.34)
Intimate partner	Ref: good	
Moderate	0.97 (0.36, 2.63)	2.20 (0.97, 4.99)
Conflict	0.81 (0.32, 2.08)	2.13 (1.54, 2.96)
Anxiety 14	Ref: no	
Yes	1.48 (1.09, 2.01)	2.30 (1.65, 3.19)
Depression 14	Ref: no	
Yes	1.58 (1.11, 2.23)	1.53 (1.11, 2.11)
Father mental prob.	Ref: never	
Before 5 years	1.99 (1.32, 2.99)	1.77 (1.14, 2.75)
After 5 years	1.31 (0.84, 2.03)	1.05 (0.64, 1.72)

Note: Zbwt (continuous *z*-score of birth weight internally adjusted for gestational age and gender).

$\beta = 2.84$ [0.77, 4.90]; at 6 months $\beta = 1.92$ [0.38, 3.46]; at 5 years $\beta = 1.94$ [0.51, 3.36]; ongoing all $\beta = 1.75$ [0.17, 3.33]). We repeated this analysis using square-root transformations as our outcomes exhibited some skewness. Results did not differ substantively (results available from corresponding author). The attrition analysis showed that those lost to follow-up were more likely to be female, have younger mothers, and have mothers who smoked at baseline. Baseline depressive, anxious, and stress symptoms did not change (Supporting Information Table S2). When we replicated our analysis with the imputed datasets, the fully adjusted odds ratio for the relationship between prenatal depressive, anxious, and stress symptoms with the internalizing 10% cutoff was similar, but the lower confidence limit crossed the null (OR = 1.54 [0.97, 2.42]), whereas the corresponding beta for the internalizing continuous outcome remained highly significant ($\beta = 2.10$ [0.97, 3.23]; for full results see Supporting Information Table S3).

DISCUSSION

By investigating the longitudinal, empirical relationships among maternal depressive, anxious, and stress symptoms across time, we identified a group of women who exhibited high levels of these symptoms only during pregnancy, and found only this group predicted adolescent internalizing behavior. This indicates not only the significance of the prenatal period, but also points to the importance of not focusing on depression, anxiety, or stress in isolation.[26] Existing research has tested outcomes among preadolescent children[13] mostly reliant on maternal or teacher reports,[3,14–16] with the former likely to be biased by the mother's own mental health.[18] Only two previous studies conducted on a small sample of adolescents have tested the hypothesis in adolescent offspring. Our study supports evidence from one of these studies, which found a strong relationship between maternal prenatal depression and adolescent depression.[46] A second study found no links with adolescent emotional or behavioral disorders at age 16,[47] however, the small sample size and the use of maternal clinical diagnoses meant this study may have lacked the necessary statistical power to detect a significant association.[47] Finally, with regard to our trajectories analysis, a previous paper using a similar mixture modeling approach found no longitudinal discontinuity in maternal depression across five timepoints, but rather three constant classes each indicating a different level of depressive severity.[22] Our different results likely resulted from the substantially longer time between the measurement periods and the fewer measurement points in our study.

Another important finding in this study was the lack of an association between postnatal maternal depressive, anxious, and stress symptoms with offspring behavior problems. Alternative evidence supports a relationship between maternal postnatal mental health and offspring behavior and emotional problems.[14,47] Our conflicting findings may have resulted for two main reasons. First, some previous studies have tested for variables of depressive, anxious, or stress symptoms in isolation. Our person-centered model on the other hand found that these constructs were likely to overlap or co-occur in the majority of nonnormative individuals. This may have identified a more severely affected group of mothers during pregnancy with increased specificity to predict the outcome, and in doing so, leaving less opportunity for other factors to explain the outcome. Second, we included a range of postnatal confounding factors aimed specifically at removing any spurious relationships

TABLE 4. Logistic and linear regression showing associations between trajectories of maternal depression, anxiety, and stress with internalizing and externalizing behavior problems (10% cutoffs and continuous score expressed as OR and β, respectively, with 95% confidence intervals [CI]; $n = 3{,}925$)

Internalizing 10% Cutoff	Unadjusted OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 4 OR (95% CI)
Trajectories					
Prenatal	**1.74 (1.13, 2.69)**	**1.66 (1.06, 2.59)**	**1.62 (1.03, 2.54)**	**1.62 (1.03, 2.54)**	**1.58 (1.01, 2.48)**
Birth	0.62 (0.22, 1.70)	0.54 (0.19, 1.51)	0.52 (0.18, 1.44)	0.52 (0.19, 1.47)	0.52 (0.19, 1.46)
6 Months	1.44 (0.91, 2.27)	1.33 (0.84, 2.11)	1.26 (0.79, 2.00)	1.26 (0.79, 2.01)	1.23 (0.76, 1.96)
5 Years	1.38 (0.94, 2.04)	1.30 (0.87, 1.93)	1.29 (0.86, 1.91)	1.24 (0.83, 1.85)	1.13 (0.75, 1.72)
Ongoing all	**1.67 (1.07, 2.59)**	1.51 (0.96, 2.39)	1.41 (0.88, 2.27)	1.36 (0.85, 2.18)	1.23 (0.75, 2.02)
Ongoing stress	**1.96 (1.16, 3.29)**	**1.84 (1.08, 3.12)**	**1.77 (1.04, 3.02)**	1.71 (1.00, 2.93)	1.69 (0.99, 2.90)
Continuous Trajectories	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
Prenatal	**2.80 (1.64, 3.95)**	**2.67 (1.54, 3.81)**	**2.55 (1.40, 3.69)**	**2.54 (1.39, 3.68)**	**2.36 (1.22, 3.51)**
Birth	0.04 (−1.77, 1.84)	− 0.35 (−2.12, 1.42)	− 0.43 (−2.20, 1.34)	− 0.39 (−2.16, 1.38)	− 0.48 (−2.24, 1.29)
6 Months	1.10 (−0.03, 2.23)	0.81 (−0.30, 1.92)	0.69 (−0.43, 1.80)	0.69 (−0.42, 1.80)	0.44 (−0.68, 1.56)
5 Years	**1.22 (0.26, 2.18)**	**1.03 (0.10, 1.97)**	**0.97 (0.03, 1.91)**	0.89 (−0.05, 1.84)	0.43 (−0.54, 1.40)
Ongoing all	**1.91 (0.75, 3.07)**	**1.62 (0.48, 2.76)**	**1.29 (0.11, 2.47)**	**1.19 (0.01, 2.37)**	0.61 (−0.61, 1.83)
Ongoing stress	**1.80 (0.35, 3.24)**	**1.46 (0.05, 2.88)**	1.38 (−0.04, 2.80)	1.32 (−0.09, 2.74)	1.19 (−0.23, 2.61)
Externalizing 10% Cutoff	Unadjusted OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 4 OR (95% CI)
Trajectories					
Prenatal	**1.61 (1.01, 2.57)**	1.40 (0.87, 2.26)	1.28 (0.79, 2.07)	1.27 (0.78, 2.06)	1.18 (0.72, 1.92)
Birth	0.88 (0.35, 2.20)	0.81 (0.32, 2.05)	0.74 (0.29, 1.88)	0.75 (0.30, 1.91)	0.73 (0.29, 1.87)
6 Months	1.46 (0.91, 2.34)	1.31 (0.81, 2.11)	1.23 (0.75, 1.99)	1.22 (0.75, 1.99)	1.12 (0.68, 1.83)
5 Years	**1.61 (1.09, 2.37)**	1.42 (0.96, 2.10)	1.31 (0.88, 1.95)	1.27 (0.85, 1.90)	1.03 (0.68, 1.57)
Ongoing all	**1.78 (1.14, 2.80)**	1.48 (0.93, 2.35)	1.18 (0.73, 1.92)	1.15 (0.70, 1.87)	0.89 (0.54, 1.49)
Ongoing stress	1.00 (0.90, 2.34)	0.98 (0.49, 1.99)	0.87 (0.43, 1.78)	0.86 (0.42, 1.76)	0.84 (0.41, 1.71)
Continuous Trajectories	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
Prenatal	**1.71 (0.60, 2.82)**	**1.17 (0.07, 2.27)**	0.97 (−0.13, 2.07)	0.95 (−0.15, 2.05)	0.76 (−0.35, 1.86)
Birth	− 0.38 (−2.12, 1.35)	− 0.61 (−2.31, 1.10)	− 0.77 (−2.48, 0.93)	− 0.73 (−2.43, 0.98)	− 0.80 (−2.50, 0.90)
6 Months	**1.20 (0.12, 2.29)**	0.82 (−0.25, 1.89)	0.71 (−0.37, 1.78)	0.72 (−0.36, 1.79)	0.47 (−0.61, 1.55)
5 Years	**2.13 (1.22, 3.05)**	**1.74 (0.84, 2.64)**	**1.58 (0.67, 2.48)**	**1.47 (0.57, 2.38)**	0.90 (−0.04, 1.83)
Ongoing all	**1.98 (0.87, 3.08)**	**1.27 (0.17, 2.380**	0.78 (−0.35, 1.92)	0.65 (−0.48, 1.79)	− 0.06 (−1.23, 1.11)
Ongoing stress	0.12 (−1.26, 1.50)	− 0.02 (−1.39, 1.35)	− 0.17 (−1.54, 1.20)	− 0.24 (−1.61, 1.13)	− 0.36 (−1.73, 1.00)

Covariates were added to the analyses in the following order: Model 1, maternal smoking/alcohol use at first clinic visit (FCV) and birth, maternal age at FCV, parity, birth weight *z*-score, maternal education and offspring gender; Model 2, model 1 + maternal life events, partner relationship quality, and attitudes toward baby at birth; Model 3, model 2 + father's mental health problem; Model 4, model 3 + maternal anxiety and depression at child age 14.
Significant OR and β bolded.

between postnatal depressive, anxious, and stress symptoms with offspring behavior (Table 4).

Because we also adjusted for a range of prenatal confounders, our analysis provides perhaps the strongest suggestion yet that prenatal depressive, anxious, and stress symptoms influence offspring behavior via a biological mechanism. This mechanism may involve increased hypothalamic–pituitary–adrenal (HPA) axis functioning caused by maternal stress as leading to lasting HPA dysregulation (i.e., programming) in the offspring, which manifests in a lifelong susceptibility to general psychopathology.[2,3] Animal studies have shown that the administration of prenatal stress increases HPA activation in the infant offspring in response to stress,[48] and prenatal stress has been associated with altered levels of HPA products in humans.[49]

Attenuation resulting from adjustment was large in these analyses. This supports existing evidence, which has also found that the relationships between prenatal mental health and offspring behavior are attenuated by environmental factors.[3,7,18] This raises the possibility that ours is a chance finding and the relationship may no longer be seen after accounting for factors we were not able to measure in this study. In order to explore further the robustness of our findings, we conducted additional linear regression analysis, which confirmed findings from our main analyses, showing that the prenatal trajectory was associated with a substantive 24% increase of the interquartile range of the internalizing behavior score. When we changed the reference category of the predictor from the normative trajectory to the prenatal trajectory, we found it was associated with

a significant increase of around two points in internalizing score compared with all other trajectories except ongoing stress only. Thus, the more robust association established with linear regression increases confidence that the relationship appears to be clinically meaningful and unlikely to be a chance finding.

The findings of our study should be interpreted in the context of a number of limitations. First, we were unable to test the timing of maternal symptoms during pregnancy having only one measure at FCV when women were on average 18 weeks into gestation. Importantly, however, the majority of previous studies point to early pregnancy as the period when the developing fetus is most sensitive to the programming effects of prenatal anxiety and stress.[2] Second, as with previous research from large birth cohorts, we did not use clinical diagnoses of common psychiatric diagnoses. However, a recent finding suggests that in relation to depression, the use of a self-report questionnaire in place of a clinical diagnosis has little effect on results.[18] Third, it has been suggested that self-reported depression, anxiety, and perceived stress are simply indicators of maternal personality, including neuroticism and trait anxiety, and that these factors are inherited by offspring who in turn report greater behavior problems that are related to these psychological attributes.[25,50] However, personality is found to be stable across adulthood,[50] while in our sample depression, anxiety, and stress symptoms were highly variable (discontinuous) across time in 20% of mothers, which suggests that the scales we used measured state or transitory depressive, anxious, and stress symptoms. Fourth, while our measure of father's history of mental problems was retrospective and was nonspecific, the fact that this measure was associated with both predictors and outcomes gives some confidence as to its validity.

Fifth, previous work has identified that a history of conduct disorder in mothers with prenatal depression is predictive of externalizing behavior in offspring.[51] Our inability to account for conduct disorder in mothers may explain our null finding, together with the fact that the women we lost to follow-up were more likely to be younger and to engage in smoking, which may be proxies for antisocial behavior.[27] Sixth, we did not test for exposure to external stressors in pregnancy, which have been linked with offspring psychopathology.[52–54] However, mother's subjective distress resulting from an external event more strongly predicted offspring behavior problems than the external stressor in one study,[53] perhaps supporting our subjective measure of "daily" stress. Finally, as with all cohort studies, the MUSP has been subject to considerable attrition that may have biased the findings. Our attrition analysis showed that mothers lost to follow-up were no more or less likely to experience anxiety, depression, or stress at baseline, suggesting our main predictor was not biased by attrition, and education status was also not affected by attrition, suggesting our results were not biased by social class.

CONCLUSIONS

In summary, we provide some of the strongest evidence for a programming effect, showing the combination of prenatal depressive, anxious, and stress symptoms has a direct impact upon adolescent offspring internalizing behavior problems. In considering the clinical implications of our research, it is important to emphasize that our findings do not only reinforce the need for intervention programs that target maternal psychopathology during pregnancy, but should refocus such efforts to target women with co-occurring symptoms across a number of constructs rather than targeting a single psychopathology. Future research based on this or similar large birth cohort studies should extend our findings by investigating how early trajectories of maternal symptoms impact on a broader range of outcomes at later stages of development.

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Conflict of interest. All authors declare no conflicts of interest.

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The relationship between maternal depressive, anxious and stress symptoms during pregnancy and adult offspring behaviour problems

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Betts, K. S., Williams, G. M., Najman, J. M. & Alati, R. (2014). The relationship between maternal depressive, anxious, and stress symptoms during pregnancy and adult offspring behavioral and emotional problems. *Depression and anxiety*.

Study purpose: As the previous study found a surprisingly robust association between maternal psychopathology during pregnancy and adolescent psychopathology, the hypothesis was extended to the adult sample. This required a revised methodological approach due to the additional loss to follow-up in the adult offspring sample when compared with the adolescent offspring sample.

Supplementary material: Some information relevant to this study (i.e., attrition, IPW and MMI analyses) was published online in a supplementary section only and can be accessed at: http://onlinelibrary.wiley.com/doi/10.1002/da.22272/suppinfo

Research Article

THE RELATIONSHIP BETWEEN MATERNAL DEPRESSIVE, ANXIOUS, AND STRESS SYMPTOMS DURING PREGNANCY AND ADULT OFFSPRING BEHAVIORAL AND EMOTIONAL PROBLEMS

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Background: *Prenatal maternal depressive, anxious, and stress symptoms have been found to be associated with child and adolescent behavior problems. In this paper, we investigate their impact on behavior problems and depressive symptoms in adulthood.* **Methods:** *Participants included 3,099 mother–offspring pairs from the Mater University Study of Pregnancy (MUSP), an Australian based, prebirth cohort study. We used latent class growth analysis (LCGA) with parallel processes to identify trajectories of maternal depressive, anxious, and stress symptoms over four time periods between the mothers' first clinic visit and 5 years postpregnancy. We fitted the estimates from the maternal trajectories in multivariate logistic regression models to predict internalizing and externalizing behavior at age 21. We adjusted for a wide range of prenatal and postnatal factors, including maternal life events, relationship quality, contact with the new born, as well as concurrent maternal depressive and anxious symptoms and father's history of mental health problem.* **Results:** *LCGA found seven groups of mothers; one group of mothers exhibited high levels of depressive, anxious, and stress symptoms during pregnancy but not at later time points. Their offspring experienced increased levels of behavior problems and depressive symptoms.* **Conclusions:** *This paper provides the first evidence that high levels of maternal subjective depressive, anxious, and stress symptoms experienced in early pregnancy may predict internalizing and externalizing behavior problems and depressive symptoms in young adults. Depression and Anxiety 00:1–10, 2014.*

Key words: *prenatal depression; anxiety and stress; latent class growth analysis; internalizing; externalizing; adult offspring*

INTRODUCTION

Experimental evidence from animal models suggests that fetal development may be altered in response to a number of maternal exposures. These include

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maternal nutrient restriction and stress that are found to have an adverse effect on offspring functioning across multiple domains, including metabolic, cardiovascular, adiposity, cognitive, and behavior.[1–3] In humans, observational evidence has repeatedly found that nutrient restriction and impaired fetal growth negatively impacts metabolic and cardiovascular functioning in adult offspring.[4,5] There is also initial evidence that maternal prenatal stress and mood disorders may impact on human offspring mental health,[1,6] however, it is unclear whether these prenatal associations exert a direct influence on offspring mental health later in life or are confounded or moderated by genetic, environmental, or other factors. Other methodological issues specific to this research area include reporting biases by maternal reports of her own and her offspring's mental health; difficulties in separating transient maternal depressive, anxious, or stress symptoms from personality traits; and problems relating underlying biological mechanisms to subjective psychological measures.[7]

Evidence of an association between stressful events outside mothers' control with adult offspring psychiatric outcomes circumvent the first two limitations, showing that prenatal exposure to earthquake, flood, famine, military invasion, and death of a relative increase the risk for adult offspring affective, psychotic, and autism disorders.[8–14] The value of these studies is in offering a robust methodology. However, these events are rare, and unpredictable, which means the potential for public health intervention is low, whereas the experience of subjective maternal mental health problems during pregnancy have a far higher prevalence in Western countries and thus potentially represent a substantial and addressable risk factor for offspring mental health problems.

The majority,[15–20] but not all,[21,22] studies support the notion that maternal symptoms of depression, anxiety, and stress during pregnancy negatively impact childhood development, leading to increased risk of attention and behavioral problems, psychopathology, and internalizing and externalizing disorders.[15–20] Aside from a recent study that investigated the relationship between maternal and offspring depression at age 18,[23] there is little available evidence that these relationships persist into adulthood. Yet, according to the developmental origins of disease theory, developmental plasticity decreases with age, while risk of illness increases as the maladaptive systems set down over early development respond to cumulative environmental exposures.[5] Animal studies have shown that the programming effect of maternal diet during pregnancy becomes stronger in rodent offspring as age advances with regard to aspects of metabolic syndrome.[24] Although no animal studies have examined if the increased risk of offspring behavior abnormalities due to prenatal stress similarly increases with age, the prevalence of anxiety and depressive disorders in humans is greater in early adulthood than in childhood or adolescence.[25] Thus, it is possible that the programming impact of prenatal psychopathology on offspring mental health may continue to be seen in early adulthood.

In this study, we extend previous research from our group into the relationship of maternal prenatal depressive, anxious, and stress symptoms with behavior in adolescent offspring,[26] and explore the association in early adulthood. We will derive empirical trajectories of maternal depressive, anxious, and stress symptoms across four time points, from pregnancy to child aged 5. This will allow us to ascertain the sensitive periods at which these symptoms increase the risk of adult offspring behavior and depressive symptoms and establish the importance of prenatal symptoms relative to those occurring at postnatal time points. In addition, this method allows us to account for the empirical and theoretical overlap between the three constructs of depression, anxiety, and stress. As in our previous study, we aim to identify a more severely affected group of mothers with psychological disturbance across multiple constructs thereby testing more robust associations with offspring behavior and depressive symptoms.[27,28] Lastly, we adjust for a number of important confounders, including fathers' history of mental problems, maternal postnatal negative life events and intimate partner conflict, and maternal infant rearing.

METHODS

PARTICIPANTS

Data were taken from the Mater University Study of Pregnancy (MUSP), a prospective prebirth cohort study following mothers and their children for over 20 years. Between 1981 and 1984 7,223 mothers attending their first clinic visit (FCV) at Brisbane's Mater Misericordiae Hospital were recruited, with subsequent follow-ups at birth, and child age 6 months, and 5, 14, and 21 years. As the baseline sample was restricted to public patients, the MUSP is skewed toward those of lower sociodemographic backgrounds (i.e., lower age, education, and income), and were more likely to smoke and be unmarried during pregnancy than the Brisbane average.[29] The trajectories analysis was conducted on 6,811 mothers, while the regression analyses were restricted to 3,099 mother–offspring pairs with complete values on all variables of interest.

MEASUREMENT OF MATERNAL DEPRESSIVE, ANXIOUS, AND STRESS SYMPTOMS

Maternal depressive, anxious, and stress symptoms were ascertained at the four time points of FCV (i.e., the prenatal measure), 3–5 days after birth, and at child 6 months and 5 years of age. Depressive and anxious symptoms were measured using the Delusions-States-Symptoms Inventory (DSSI), which includes subscales, both consisting of seven items designed to include the primary features of anxiety and depression.[30] The DSSI has been found to correlate well with other established symptoms scales including the Edinburgh Postnatal Depression Scales (EPDS) and the Hospital Anxiety/Depression Scale (HADS).[31] Stress symptoms were measured using the four-item Reeder Stress Inventory (RSI), designed to measure self-perceived daily strain resulting from the physiological and psychological reactions to personal or social situations, such as daily hassles, major events, and coping resources.[32,33] A validation study has supported the

construct validity of the RSI.[34] As in our previous study, symptoms and frequency of occurrence (5-point scale from never to always) were summed to produce dichotomized variables with the 10% of individuals with the highest scores categorized as cases.

MEASUREMENT OF ADULT OFFSPRING BEHAVIOR PROBLEMS AND DEPRESSIVE SYMPTOMS

At the 21-year follow-up, adult offspring completed the Achenbach Young Adult Self-Report (YASR).[35] We used the two summary measures, within the YASR, of internalizing and externalizing behavior problems, which are themselves made up of a number of subscales as follows: internalizing (anxiety/depression and withdrawn subscales); externalizing (aggression, delinquency, and intrusive subscales). Each question regards the experience of symptoms in the preceding 6 months and respondents answer on a 3-point scale including rarely or never /sometimes/often. Although the YASR was developed for use in adults aged 18–35 in a clinical setting, it has been validated in large population samples.[36] Also at 21 years, depressive symptoms were measured using the Centers for Epidemiological Studies Depression (CES-D) scale.[37] The CES-D comprises 20 symptoms of negative and positive affect regarding the past week, with frequency responses (less than 1 day/1–2 days/3–4 days/ 5–7 days). The CES-D was constructed using the well-known items from existing depression scales, and correlates well with other depression scales, and has been found to have good internal consistency and good short-term test–retest reliability.[37–39] In separate regression analyses, all three scales were employed first in their dimensional (continuous) form, and second as dichotomized variables with the top 10% representing clinically significant behavior problems or depressive symptoms.

CONFOUNDING VARIABLES

We adjusted for a number of a priori factors that may confound the relationship between maternal prenatal depression, anxiety, and stress with adult outcomes.[40] Maternal smoking (nonsmoker/light to moderate/heavy smoker) and alcohol consumption (abstainer/light drinker/moderate drinker/heavy drinker) during pregnancy were recorded at FCV. Birth weight, gestational age (GA), gender, and parity were taken from obstetric records at the time of birth. We used a continuous measure of birth weight *z*-scores internally adjusted for GA and gender as an indicator of fetal growth.[41–43] We adjusted for a number of factors ascertained 3–5 days after birth, which may act as intermediaries between postnatal mental health and offspring behavioral development.[44–46] These included a shortened version of The Life Events Scale,[47] including eight possible negative events (dichotomized as 0–3/4 or more), conflict between the mother and her intimate partner assessed using the Spanier Dyadic Adjustment Scale,[48] and maternal contact with newborn.[26] At 21 years, offspring education level was ascertained (incomplete secondary/complete secondary/attending or completed college or TAFE (technical college)/attending or completed university), and mothers were asked if the study child's biological father had ever seen a doctor in relation to a mental or emotional problem.

STATISTICAL ANALYSIS

We used latent class growth analysis (LCGA) symptoms with parallel processes to derive trajectories of maternal depressive, anxious, and stress symptoms across the four time points. We employed full-information maximum likelihood (FIML) with robust standard errors (MLR) available in Mplus version 6,[49] which uses a missing at random (MAR) assumption to estimate model parameters based on all available data and allows missingness to be related to variables included in the analysis.[50] To decrease bias related to estimating missing data, we excluded mothers who had more than 25% of data missing (i.e., were missing more than 3 of 12 measures), resulting in 6,811 mothers included in the trajectories analysis. We compared a number of LCGA models, from two to eight classes, including constant, linear, and quadratic growth functions, and the superior model was selected according to the Bayesian information criterion (BIC) and the bootstrap likelihood ratio test (BLRT),[51] but we were also guided by theoretical considerations (i.e., identification of a prenatal trajectory without over fitting). As in our previous study,[26] the class probabilities (trajectories) were then exported to STATA version 11 for regression analyses, a satisfactory approach with an entropy $\geq .80$.[52]

We used logistic and linear regression to separately test associations between the three outcomes (i.e., internalizing and externalizing behavior problems and depressive symptoms at 21 years) as binary and continuous dependent variables with confounders. We then used multinomial logistic regression to test associations between the trajectories with the confounding variables. Next, we tested the univariate associations between the trajectories with the outcomes before adding the covariates to make the final model. We undertook two sensitivity analyses to judge how attrition affected our findings, starting by comparing those who had been lost to follow-up with those used in our final analysis by a number of baseline variables. We subsequently used the results of the above multivariate logistic regression model to produce weights representing the inverse probability of each participant being included in the study, and replicated the final analysis using these weights. We used inverse probability weighting instead of multiple imputation because the proportion lost to follow-up (and missing data on the outcomes) was large.[53]

RESULTS

Results from the trajectories analysis suggested that a seven-class quadratic LCGA was the best fit to the data (see Supporting Information Table S1 for all fit statistics), with this model reflecting the model that was attained in the previous study using listwise deletion in place of FIML. The seven trajectories included[1] depressive, anxious, and stress symptoms during pregnancy (i.e., the prenatal group);[2] during birth;[3] at 6 months; and[4] at 5 years, in addition to[5] ongoing depressive, anxious, and stress symptoms over the entire period,[6] ongoing stress symptoms (only) over the entire period, and[7] a normative group (Fig. 1). Table 1 reveals that most confounders were associated with one or more of the binary outcomes. Birth weight, heavy smoking during pregnancy, and maternal life events at birth predicted depressive symptoms only. Although having parents with other than a good relationship at birth, not completing secondary school, and having a father with a history of mental illness were associated with all outcomes. Table 2 shows the univariate associations between the maternal trajectories and confounders. The prenatal trajectory was associated with heavy smoking during pregnancy, lower maternal age and parity, and maternal negative life events and having parents with other than a good relationship at birth.

Table 3 shows the univariate and multivariate associations between the maternal trajectories of depressive, anxious, and stress symptoms and adult internalizing and externalizing behavior and depressive symptoms. After adjustment for confounders, the prenatal trajectory

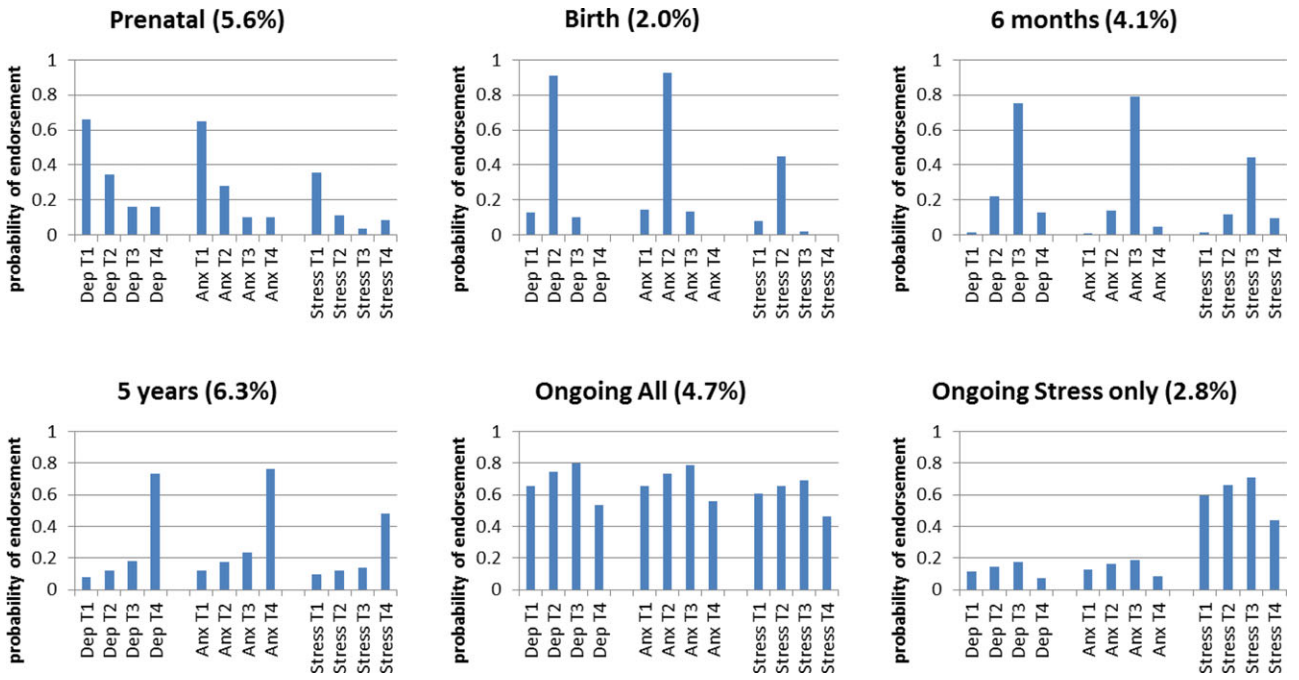

Figure 1. Seven-class LCGA solution showing the probability of each of the six nonnormative classes of endorsing depression (Dep), anxiety (Anx), and stress (Stress) at each time point—pregnancy (T1), birth (T2), child 6 months (T3), child 5 years (T4). Classes are labeled depending on the time point/s at which they exhibit the strongest probability of endorsement with the percentage of the sample in each class shown in parenthesis (the normative class represented 74.5% of the sample and is shown in the Supporting Informations Results section). Model fit indices: BIC = 40,025; Entropy = .87; BLRT < .001 (Supporting Information Table S3 contains comprehensive fit indices for all tested models).

predicted all three outcomes in the linear regressions (internalizing, $\beta = 2.76$ [1.33, 4.19]; externalizing, $\beta = 1.45$ [0.28, 2.62]; depressive symptoms, $\beta = 2.34$ [0.85, 3.83]) and depressive symptoms in logistic regressions (OR = 1.87 [1.27, 2.73]). Ongoing maternal depressive, anxious, and stress symptoms predicted internalizing behavior and depressive symptoms in linear regression (internalizing, $\beta = 2.17$ [0.51, 3.84]; depressive symptoms, $\beta = 3.54$ [1.80, 5.28]), and depressive symptoms in logistic regression (depressive symptoms, OR = 1.99 [1.29, 3.09]). Ongoing stress only predicted internalizing behavior in linear regression (internalizing, $\beta = 1.83$ [0.06, 3.59]). Interestingly, even before adjustment mothers who had high levels of depressive, anxious, or stressed symptoms at birth, 6 months or 5 years of child age did not predict any outcomes. Attrition analysis revealed that mothers lost to follow-up were more likely to belong to the groups with prenatal and ongoing depressive, anxious, and stress symptoms (Supporting Information Table S2), but not any of the other groups. The inverse probability analysis replicated all the associations in the main analysis (Supporting Information Table S3). Although the effect sizes did not alter substantively, three estimates gained significance due to the weights, including associations between the ongoing all group with externalizing (binary outcome), and the prenatal and ongoing all group with internalizing (binary outcomes).

DISCUSSION

This is the first study to provide evidence of an association between prenatal psychopathology and behavioral problems in adulthood, comparing well with a recent study finding maternal depression predicted offspring depression at age 18.[23] Similar associations have been found extensively in childhood and early adolescence;[15–20] findings from this paper suggest that such associations are likely to extend past adolescence. Our results based on subjective psychopathology during pregnancy compare well with findings that stressful life events during pregnancy predict mental health problems in adult offspring.[8–14] In addition, we found that depressive, anxious, and stress symptoms expressed together during pregnancy and predicted all mental health outcomes among adult offspring after adjustment for a number of important confounding variables.[27,28]. Conversely there were no associations with adult offspring mental health in groups exposed to maternal depressive, anxious, and stress symptoms only during postnatal development, which may suggest a biological mechanism is responsible for the association.

The main aim of our study was to determine whether maternal prenatal depressive, anxious, and stress symptoms had the potential to increase the risk of behavioral problems and depressive symptoms in adult offspring via a biological process in utero by eliminating alternate

TABLE 1. Logistic regression showing associations between adolescent reported internalizing and externalizing behavior problems at 21 with confounding variables (expressed as OR with 95% confidence intervals [CI]; $n = 3{,}099$)

YSR scales (10%)	Prevalence *n* (%)	Internalizing OR (95% CI)	Externalizing OR (95% CI)	Depressive sym. OR (95% CI)
Covariables				
Gender				
Male	1,452 (46.9)	1.00	1.00	1.00
Female	1,647 (53.1)	1.67 (1.30, 2.15)	0.57 (0.44, 0.74)	1.72 (1.45, 2.04)
Mat smoke preg.				
None	2,088 (67.4)	1.00	1.00	1.00
Light/moderate	798 (25.7)	1.22 (0.92, 1.60)	1.59 (1.21, 2.09)	1.21 (1.00, 1.46)
Heavy	213 (6.9)	1.52 (0.99, 2.34)	1.28 (0.79, 2.09)	1.78 (1.32, 2.42)
Mat alc. preg.	3,099 (100)	0.98 (0.81, 1.20)	1.03 (0.84, 1.27)	1.02 (0.89, 1.17)
Zbwt	3,099 (100)	0.91 (0.80, 1.03)	1.09 (0.96, 1.23)	0.92 (0.84, 0.99)
Mothers' age	3,099 (100)	0.98 (0.96, 1.01)	0.96 (0.94, 0.99)	0.99 (0.97, 1.01)
Parity	3,099 (100)	0.94 (0.84, 1.05)	0.87 (0.77, 0.98)	1.05 (0.97, 1.12)
Newborn contact				
Wanted	2,642 (85.3)	1.00	1.00	1.00
Borderline	235 (7.6)	1.00 (0.63, 1.58)	0.90 (0.55, 1.47)	0.92 (0.67, 1.27)
Not wanted	222 (7.1)	1.12 (0.71, 1.76)	0.64 (0.36, 1.13)	1.07 (0.78, 1.47)
Mother life events				
0–3	2,956 (95.4)	1.00	1.00	1.00
Four or more	143 (4.6)	1.13 (0.65, 1.96)	1.06 (0.59, 1.91)	1.52 (1.06, 2.19)
Intimate partner				
Good	2,723 (87.9)	1.00	1.00	1.00
No partner	91 (2.9)	1.54 (0.83, 2.87)	2.26 (1.28, 3.99)	1.53 (0.97, 2.41)
Moderate	252 (8.1)	1.53 (1.04, 2.26)	1.26 (0.81, 1.95)	1.55 (1.16, 2.05)
Conflict	33 (1.1)	1.02 (0.31, 3.35)	3.66 (1.63, 8.21)	1.97 (0.96, 4.03)
Offspring's education				
University	127 (4.1)	1.00	1.00	1.00
College/TAFE	700 (22.6)	1.50 (0.70, 3.20)	3.60 (1.11, 11.67)	1.96 (1.14, 3.37)
High school	1,667 (53.8)	1.35 (0.65, 2.83)	3.29 (1.03, 10.50)	1.74 (1.03, 2.95)
Incomp. high school	605 (19.5)	2.30 (1.08, 4.88)	6.76 (2.10, 21.72)	3.10 (1.81, 5.31)
Father mental prob.				
No	2,639 (85.2)	1.00	1.00	1.00
Yes	460 (14.8)	1.41 (1.03, 1.92)	1.44 (1.04, 1.98)	1.56 (1.25, 1.94)

possibilities, including postnatal exposure, and important prenatal and postnatal covariates. Thus, underlying our findings may be a mechanism by which alterations in the mothers' hypothalamic-pituitary-adrenal (HPA) axis, due to the experience of depressive, anxious, and stress symptoms, impact the developing fetal HPA axis, programming it to a permanent state of dysregulation, and thus increasing the risk for a number of psychopathological and behavioral conditions in later life.[7] Animal studies have shown that the administration of prenatal stress increases HPA activation in the offspring,[54] and prenatal stress has been associated with altered levels of HPA products in humans.[55] However, the ways in which a change in maternal psychological state is transmitted to the fetus remains unknown, with studies showing the fetal heart rate increases within seconds of disruptions to the maternal environment, long before the products of the HPA-axis could elicit such a reaction.[7]

Our method and unique data led to a number of other interesting findings that add context to the main relationship. First, as we proposed in a prior study,[26] except for a group of mothers exhibiting ongoing stress only, the three constructs of depressive, anxious, and stress symptoms expressed together. Considering the positive relationship between comorbid conditions and symptoms severity,[28] the strength of our association across 21 years of offspring development may rely on us having identified a group of mothers with relatively severe symptoms of mental illness in pregnancy. Considering this, and the empirical and theoretical overlap between these constructs,[7] future studies should not limit themselves to a single construct of mental problems in pregnancy. Second, we identified discontinuous trajectories of maternal depressive, anxious, and stress symptoms, which aside from making it possible to test a hypothesis regarding the period at which offspring may be most sensitive to the effect, also increased confidence that our measures did not simply represent stable measures of personality that have a strong genetic component.[27,56]

One group of mothers exhibited ongoing symptoms across all constructs and time points, and their offspring experienced increases in behavioral problems and depressive symptoms after adjustment for confounders. It is possible that the ongoing nature of the depressive, anxious, and stress symptoms in these mothers

TABLE 2. Multinomial logistic regression of the univariate associations between maternal trajectories of depression, anxiety, and stress, and stress only with confounding variables (expressed as OR with 95% confidence intervals [CI]; $n = 3,099$)

	Discontinuous Dep/Anx/Stress trajectories				Ongoing Dep/Anx/Stress trajectories	
Trajectories	Prenatal OR (95% CI)	Birth OR (95% CI)	6 Months OR (95% CI)	5 Years OR (95% CI)	Distress OR (95% CI)	Stress only OR (95% CI)
Gender			Ref.—male			
Female	1.11 (0.78, 1.58)	1.41 (0.81, 2.56)	1.02 (0.70, 1.49)	1.08 (0.81, 1.44)	1.10 (0.74, 1.66)	1.07 (0.69, 1.65)
Mat smoke preg.			Ref.—none			
Light/moderate	1.57 (1.05, 2.35)	1.70 (0.96, 3.04)	1.16 (0.75, 1.79)	1.46 (1.06, 2.01)	1.24 (0.76, 2.02)	0.84 (0.49, 1.46)
Heavy	5.21 (3.20, 8.48)	1.79 (0.62, 5.14)	2.11 (1.09, 4.09)	2.35 (1.41, 3.90)	5.12 (2.97, 8.84)	2.47 (1.23, 4.96)
Mat alc preg.	0.96 (0.72, 1.28)	0.78 (0.48, 1.25)	1.23 (0.91, 1.65)	0.95 (0.75, 1.21)	1.16 (0.84, 1.60)	1.17 (0.83, 1.66)
Zbwt	0.84 (0.69, 1.00)	0.88 (0.66, 1.16)	0.89 (0.73, 1.08)	1.00 (0.86, 1.16)	0.96 (0.77, 1.18)	1.12 (0.90, 1.39)
Mothers' age	0.92 (0.88, 0.96)	0.97 (0.91, 1.02)	0.98 (0.94, 1.02)	0.98 (0.95, 1.01)	1.03 (0.99, 1.07)	1.04 (1.00, 1.09)
Parity	0.77 (0.64, 0.93)	1.03 (0.81, 1.30)	1.04 (0.88, 1.22)	1.11 (0.99, 1.25)	1.33 (1.15, 1.54)	1.34 (1.15, 1.56)
Newborn contact			Ref.—wanted			
Borderline	1.16 (0.62, 2.20)	1.86 (0.83, 4.19)	1.25 (0.62, 2.53)	1.15 (0.67, 1.96)	0.78 (0.31, 1.94)	2.35 (1.24, 4.45)
Not wanted	1.24 (0.64, 2.42)	0.62 (0.15, 2.60)	2.94 (1.72, 5.01)	1.43 (0.85, 2.42)	2.92 (1.66, 5.13)	2.30 (1.16, 4.59)
Mother life events			Ref.—0–3			
Four or more	5.97 (3.51, 10.16)	4.25 (1.76, 10.27)	4.04 (2.12, 7.70)	2.37 (1.28, 4.36)	8.18 (4.70, 14.26)	1.72 (0.61, 4.84)
Intimate partner			Ref.—good			
No partner	4.36 (2.72, 7.01)	2.04 (0.48, 8.66)	1.22 (0.38, 3.98)	1.43 (0.61, 3.38)	5.72 (2.71, 12,07)	1.17 (0.28, 4.91)
Moderate	4.36 (2.71, 7.01)	5.55 (2.89, 10.67)	2.39 (1.33, 4.30)	2.91 (1.89, 4.47)	5.86 (3.49, 9.82)	3.20 (1.72, 5.94)
Conflict	5.94 (1.95, 18.10)	3.63 (0.47, 28.09)	1.45 (0.19, 11.07)	2.56 (0.74, 8.86)	13.57 (5.13, 35.88)	4.18 (0.94, 18.56)
Offspring's education			Ref.—university			
College/TAFE	2.00 (0.60, 6.67)	1.16 (0.26, 5.27)	1.74 (0.52, 5.85)	0.78 (0.36, 1.66)	5.62 (0.76, 41.70)	1.16 (0.37, 4.02)
High school	1.92 (0.60, 6.21)	1.04 (0.24, 4.51)	1.39 (0.43, 4.53)	0.91 (0.45, 1.85)	3.69 (0.50, 27.00)	1.26 (0.38, 4.10)
Incomp. high school	2.24 (0.67, 7.05)	1.68 (0.38, 7.50)	2.48 (0.74, 8.26)	1.41 (0.68, 2.95)	5.28 (0.70, 39.58)	1.20 (0.34, 4.22)
Father mental prob.			Ref.—no			
Yes	1.01 (0.61, 1.66)	1.39 (0.69, 2.79)	1.16 (0.69, 1.940	1.43 (0.99, 2.07)	1.67 (1.01, 2.74)	1.24 (0.69, 2.79)

represented a genetic predisposition (e.g., neuroticism and trait anxiety) that was inherited by their offspring (i.e., genetic continuity). Future research is needed to progress this line of research to ultimately identify which aspect of offspring behavior problems is inherited from that which is programmed. Inconsistently with previous research, we did not find that postnatal psychopathology predicted offspring outcomes even prior to covariate adjustment. It may be that the most severe postnatal psychopathology was captured in the group of mothers with ongoing or persistent psychopathology throughout the study period, while exposure at a single time point did not have a lasting effect on offspring adult outcomes. Though it is also possible that early postnatal exposure to maternal psychopathology is not predictive of the outcomes we measured after adolescence, with further research needed to confirm these possibilities. In addition, we found a single weaker association between mothers who exhibited high levels of subjective stress only at all time points with offspring internalizing behavior. Although we cannot rule out that this was a chance finding, it is interesting to consider that there may be a separate pathway to adult internalizing via ongoing maternal stress, and further research could explore this possibility. Lastly, the association between prenatal depressive, anxious, and stress symptoms with offspring behavior problems was not found to be noticeably stronger than in a similar analysis conducted on the sample when the offspring were 14 years of age,[26] or compared with the effect sizes seen in previous studies on children.[15–20] Although differing methodologies mean a formal comparison cannot be made, we did not find support for the notion that consequences of the exposure will become more apparent as age advances.[5,6,24]

Our study has a number of limitations. We were unable to account for the precise timing of maternal depressive, anxious, and stress symptoms during pregnancy. Despite evidence suggesting that early pregnancy is the most sensitive period of fetal development in relation to the outcome,[6] some evidence suggests other points in pregnancy as also important.[57] Future research should concentrate on identifying which period of prenatal exposure is the most sensitive to the development of psychopathology in young adults. Also, we relied on self-reported measures of maternal mental health symptoms rather than using a clinical diagnosis. However, a recent study suggests that when testing the developmental origins hypothesis, the use of self-reported depressive symptoms in place of a clinical diagnosis were appropriate.[58] An additional consideration is that we did not adjust for objective measures of maternal prenatal stress, which has been found as an important factor by the studies described earlier.[8–14] However, the mother's subjective distress in relation to the objective event has been found more predictive of offspring behavior than exposure to the event itself,[59] perhaps supporting the

TABLE 3. Logistic and linear regression showing associations between trajectories of maternal depression, anxiety, and stress with internalizing and externalizing behavior problems, and depressive symptoms at offspring age 21 years (10% cut offs and continuous score expressed as OR and β, respectively, with 95% confidence intervals [CI]; $n = 3,099$)

	Unadjusted analyses					
	Internalizing (10%) OR (95% CI)	Internalizing (con.) β (95% CI)	Externalizing (10%) OR (95% CI)	Externalizing (con.) β (95% CI)	Depressive symptom (10%) OR (95% CI)	Depressive symptom (con.) β (95% CI)
Trajectories						
Prenatal	1.74 (1.05, 2.88)	2.99 (1.57, 4.41)	1.55 (0.91, 2.63)	2.07 (0.91, 3.24)	2.12 (1.47, 3.05)	2.81 (1.32, 4.29)
Birth	1.31 (0.56, 3.11)	−0.38 (−2.58, 1.82)	0.63 (0.19, 2.03)	−0.89 (−2.70, 0.92)	1.13 (0.60, 2.12)	0.35 (−1.95, 2.65)
6 months	0.80 (0.38, 1.67)	0.54 (−1.00, 2.08)	0.60 (0.26, 1.38)	−0.05 (−1.31, 1.22)	1.06 (0.68, 1.67)	0.38 (−1.23, 1.99)
5 years	1.37 (0.86, 2.16)	0.69 (−0.49, 1.86)	0.87 (0.50, 1.49)	0.64 (−0.33, 1.61)	1.16 (0.83, 1.62)	1.23 (0.00, 2.46)
Ongoing all	1.90 (1.08, 3.35)	2.70 (1.05, 4.35)	1.78 (0.99, 3.19)	2.13 (0.78, 3.49)	2.46 (1.62, 3.72)	4.38 (2.66, 6.12)
Stress only	1.61 (0.84, 3.08)	1.96 (0.18, 3.75)	0.68 (0.27, 1.71)	0.66 (−0.81, 2.12)	1.28 (0.78, 2.11)	1.14 (−0.73, 3.01)
	Adjusted analyses					
	Internalizing (10%) OR (95% CI)	Internalizing (con.) β (95% CI)	Externalizing (10%) OR (95% CI)	Externalizing (con.) β (95% CI)	Depressive symptom (10%) OR (95% CI)	Depressive symptom (con.) β (95% CI)
Trajectories						
Prenatal	1.53 (0.90, 2.60)	2.76 (1.33, 4.19)	1.30 (0.74, 2.27)	1.45 (0.28, 2.62)	1.87 (1.27, 2.73)	2.34 (0.85, 3.83)
Birth	1.12 (0.47, 2.69)	−0.95 (−3.12, 1.23)	0.57 (0.17, 1.87)	−1.37 (−3.15, 0.42)	0.94 (0.49, 1.79)	−0.30 (−2.57, 1.97)
6 months	0.72 (0.34, 1.51)	0.37 (−1.19, 1.86)	0.55 (0.23, 1.28)	−0.40 (−1.65, 0.84)	0.94 (0.59, 1.48)	−0.08 (−1.67, 1.51)
5 years	1.23 (0.77, 1.96)	0.36 (−0.81, 1.52)	0.77 (0.44, 1.35)	0.22 (−0.73, 1.18)	1.01 (0.71, 1.43)	0.78 (−0.44, 2.00)
Ongoing all	1.73 (0.95, 3.13)	2.17 (0.51, 3.84)	1.59 (0.85, 2.96)	1.33 (−0.04, 2.69)	1.99 (1.29, 3.09)	3.54 (1.80, 5.28)
Stress only	1.63 (0.84, 3.16)	1.83 (0.06, 3.59)	0.71 (0.28, 1.80)	0.53 (−0.92, 1.98)	1.21 (0.73, 2.02)	0.97 (−0.87, 2.82)

Model adjusted for maternal smoking/alcohol use at first clinic visit (FCV), maternal age at FCV, parity, birth weight z-score, offspring gender, maternal life events, partner relationship quality and attitudes toward baby at birth, father's mental health problem, and offspring education.
10%, binary behavior outcome for logistic regression, highest scoring 10% represents caseness; con., continuous behavior outcome for linear regression.

inclusion of subjective stress measure. Finally, we encountered considerable attrition in our sample, which may have biased our findings. As the attrition analysis revealed that mothers who were excluded from the final model by loss to follow-up were more likely to belong to the groups with prenatal and ongoing depressive, anxious, and stress symptoms, we used inverse probability weighting as one method to correct for this bias. We found all the associations from the main analysis were replicated, and several associations involving the prenatal and all ongoing groups, which had been borderline in the main analysis, were now significant (described in Results). These findings suggest that the relationship between these two groups of mothers and offspring behavior problems could even be stronger had we retained the entire sample.

Using data from a prospective, prebirth cohort study, we found evidence to suggest that in utero exposure to a combination of prenatal depressive, anxious, and stress symptoms increases the risk of behavioral problems and depressive symptoms in early adulthood. The modest magnitude of the effect sizes, the substantial attenuation resulting from covariate adjustment, and evidence from previous research,[44,45] all suggest that the increased risk of offspring mental health problems posed by prenatal psychopathology is also likely to depend on a number of other risk factors along this "causal" pathway. Thus, future research is needed, which explores the role of potential moderating and mediating factors to identify subgroups in which prenatal psychopathology most strongly impacts on offspring development. For now, these findings suggest that a focus on maternal mental health during pregnancy may not only be beneficial to women's obstetric outcomes, but also helps in reducing the prevalence of mental health problems in young adults.[60]

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Chapter 6 - Stress and illness during pregnancy as determinants of offspring psychosis vulnerability

Exposure to stressful life events during pregnancy predicts psychotic experiences via behaviour problems in childhood

Published manuscript and formal citation

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Study purpose: This study aimed to test whether the increased psychotic experiences in later life attributable to maternal stress during pregnancy were mediated via early general behaviour problems in childhood.

Supplementary material: Some information relevant to this study (i.e., attrition, IPW and MMI analyses) was published online in a supplementary section only and can be accessed at: http://www.sciencedirect.com/science/article/pii/S0022395614002374

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Exposure to stressful life events during pregnancy predicts psychotic experiences via behaviour problems in childhood

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ABSTRACT

Background: Exposure to stressful life events during pregnancy has been associated with later schizophrenia in offspring. We explore how prenatal stress and neurodevelopmental abnormalities in childhood associate to increase the risk of later psychotic experiences.

Methods: Participants from the Mater University Study of Pregnancy (MUSP), an Australian based, prebirth cohort study were examined for lifetime DSM-IV positive psychotic experiences at 21 years by a semi-structured interview ($n = 2227$). Structural equation modelling suggested psychotic experiences were best represented with a bifactor model including a general psychosis factor and two group factors. We tested for an association between prenatal stressful life events with the psychotic experiences, and examined for potential moderation and mediation by behaviour problems and cognitive ability in childhood.

Results: Prenatal stressful life events predicted psychotic experiences indirectly via behaviour problems at child age five years, and this relationship was not confounded by maternal stressful life events at child age five. We found no statistical evidence for an interaction between prenatal stressful life events and behaviour problems or cognitive ability.

Conclusion: The measurable effect of prenatal stressful life events on later psychotic experiences in offspring manifested as behaviour problems by age 5. By identifying early abnormal behavioural development as an intermediary, this finding further confirms the role of prenatal stress to later psychotic disorders.

1. Objectives

Schizophrenia and other psychotic disorders are increasingly being understood as the severe and disabling end point of a continuous distribution of psychotic experiences present in the general population (Linscott and Van Os, 2010; Subramaniam et al., 2013). The neurodevelopmental model of schizophrenia posits that a number of environmental and genetic factors, either via accumulation or through more complex interactions, are responsible for an individual's movement along this continuum from transitory and relatively harmless psychotic experiences towards a clinical diagnosis (Rapoport et al., 2012; Van Os et al., 2009). The earliest environmental risk factors may interrupt normal brain development during fetal life, when the central nervous system is at a critical stage of formation, and are perhaps responsible for priming an individual toward an atypical trajectory of neurodevelopment increasing the risk of later schizophrenia (King et al., 2010; Meli et al., 2012; Meyer and Feldon, 2010). A number of epidemiological studies have shown that exposure to objective stressors during gestation, including death of a relative, military invasion and natural disasters, increase the risk for schizophrenia and other psychotic disorders in adult offspring (Khashan et al., 2008; Van Os and Selten, 1998; Selten et al., 1999; Malaspina et al., 2008). These findings are supported by animal studies which show that associations between induced prenatal stress in rats and offspring schizophrenia-like behaviour are accompanied by neuroendocrine abnormalities (Meyer and Feldon, 2010).

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The neurodevelopmental model of schizophrenia is also consistent with findings that the condition is preceded by abnormalities in cognitive and motor development, and behavioural problems (Bearden et al., 2000; Woodberry et al., 2008; Walker et al., 1994; Welham et al., 2009). Previous studies have examined how these premorbid developmental abnormalities are associated with prenatal and perinatal environmental risk factors to increase later schizophrenia risk. However, evidence so far supports two separate interpretations of the resulting process, depending on whether the developmental abnormalities are viewed as the inevitable premorbid manifestation of a genetic predisposition to later schizophrenia, (Bearden et al., 2000; Cannon et al., 2002a), or if they are affected by prenatal environmental risk factors (Brown et al., 2001; Ellman et al., 2009).

With regard to the former, one study used delayed motor development as a proxy for a genetic predisposition to schizophrenia along with obstetric complications to implicate gene × environment interactions (Van Os et al., 2008) as playing a central role in the neurodevelopment of schizophrenia and related disorders (Clarke et al., 2011). Such an interaction is in line with the 'two-hits' hypothesis of schizophrenia, whereby an early environmental exposure can increase the risk of schizophrenia in those genetically susceptible, who may be identified by prodromal neurodevelopmental abnormalities, as is the case in the study by van Os (Van Os et al., 2008). Alternatively, studies supporting the latter view, see premorbid developmental abnormalities as part of the developmental sequelae resulting from prenatal exposures such as infection, which also increases the risk for schizophrenia, thus concluding that developmental abnormalities play a mediating role via which prenatal infection impacts schizophrenia risk (Brown et al., 2001; Ellman et al., 2009). With uncertainty remaining, further longitudinal studies are needed which can properly test both possibilities using statistical tests to assess possible mediating or moderating effects, as the findings will have important implications for our understanding of the neurodevelopmental model of schizophrenia (Khandaker et al., 2013), and are likely to inform preventative strategies.

To date, no study has investigated how prenatal stress and cognitive development or behaviour problems in childhood associate to predict later schizophrenia or psychotic illness. In this study we employ structural equation modelling to examine if the effect of prenatal stressful life events on psychosis experiences measured in early adulthood is moderated or mediated by behavioural problems or cognitive ability at child age five years. We use a latent factor of psychotic experiences as our outcome because a continuous outcome holds more statistical information than a binary diagnosis, giving us greater power to detect moderation and mediation effects. In addition, evidence suggests that 'psychosis' is better represented as a dimensional phenotype (Zammit et al., 2013; Ahmed et al., 2012; Subramaniam et al., 2013) rather than as categorical diagnoses, and subthreshold psychotic experiences are influenced by similar risk factors which predict schizophrenia including premorbid developmental abnormalities (Linscott and Van Os, 2010; Van Os et al., 2009; Blanchard et al., 2010; Kelleher et al., 2013). We also adjust for a number of important confounders including additional prenatal and perinatal risks for schizophrenia and maternal stressful life events at child age five years.

2. Materials and methods

2.1. Participants

Participants came from the Mater University Study of Pregnancy (MUSP), a prospective pre-birth cohort study following mothers and their children for over 20 years. A total of 7223 mothers attending their first clinic visit at Brisbane's Mater Misericordiae Hospital were recruited between 1981 and 1984, with subsequent follow-ups at birth, and child age 6 months, and 5, 14 and 21 years. Of the original 8556 pregnant mothers who were approached, 98 refused to participate, 710 delivered at another hospital, 59 had multiple births, 55 adopted out their child and 411 infants died during pregnancy or delivery. The MMH accounted for around 50% of all births in Brisbane during the catchment period and resulted in a sample skewed towards lower socio-economic position than the Brisbane average due to the exclusion of private patients attending the MMH, further information found elsewhere (Najman et al., 2005). At 21 years 2558 offspring completed the Composite International Diagnostic Interview (CIDI-Auto 2.1) (World Health Organization, 1997), providing the sample to examine the factor structure of psychosis. The final model included participants with values on all variables of interest ($n = 2227$). Informed consent from all participants was gained, all data was coded for confidentiality and ethics was approved for the cohort by the institution and funding body.

2.2. Experiences of positive psychosis

At the 21 year follow-up the lifetime version of the CIDI-Auto (World Health Organization, 1997) was administered by trained interviewers, including items assessing positive psychotic experiences (15 delusions and 6 hallucinations). Positive responses to delusions and hallucinations were probed to increase certainty that the experience was psychotic. As the prevalence of experiences was low, it was necessary to combine three pairs of 'like' delusions [(i) being secretly tested on ($n = 13$; 0.5%)/someone was plotting to hurt you ($n = 17$; 0.6%); (ii) thoughts were inserted into your mind ($n = 23$; 0.9%)/thoughts were taken from your mind ($n = 10$; 0.4%); (iii) felt under the control of an external force ($n = 13$; 0.5%)/felt strange forces working on you ($n = 21$; 0.8%)], and exclude two delusions [(i) convinced someone you never met was in love with you ($n = 5$; 0.2%); (ii) convinced your partner was cheating on you ($n = 17$; 0.6%)], to satisfy the requirements of the covariance matrix in the resulting structural equation model (Supplementary Table 1).

2.3. Prenatal and perinatal predictors

At the first clinic visit pregnant mothers were asked how many cigarettes they had smoked in the last week (none/1–19/20+) and completed the Delusions-States Symptoms Inventory (DSSI) (Bedford and Folds, 1977), measuring seven sympotms of depression and anxiety on separate scales, with 'casesness' on both scales defined at ≥4. The DSSI has been found to correlate well with the Edinburgh Postnatal Depression Scale (EPDS) and the Hospital Depression/Anxiety Scale (Bedford and Folds, 1978). At birth, mothers were asked about the experience of eight negative life events, drawn from the Social Readjustment Rating Scale (Holmes and Rahe, 1967), having occurred in the six months (thus inclusive of the second and third trimesters) prior to giving birth including; death/illness of someone close, health problems, serious disagreements with your partner, with someone else, financial problems, major employment change of partner, serious problems with housing or accommodation and serious problems with the law (45% of the sample had experienced 0 events, 28% experienced 1 event, 15% experienced 2 events, 7% experienced 3 events, and 5% experienced 4 or more events). At birth Apgar score (<7 at 1 min), forced induction of labour, pre-eclampsia, birth weight z-score adjusted for gestational age and gender (Betts et al., 2013) (continuous and lowest 10 percentile) were collected from obstetric records, and mothers' reported whether the baby required

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"specialist medical care" (did not happen/minor problem/moderate problem/major problem).

2.4. Childhood mediators

At 5 years mothers completed a shortened version of the Achenbach Child Behaviour Checklist (CBCL) (Achenbach, 1991) assessing 10 items each from the internalising and externalising scales, and 10 items from the social/attention/thought sub-scales. The most commonly occurring behaviours were included in the shortened version, and in this study we combined the items into a total behaviour problems scale (Alpha = 0.897), and dichotomised the scale defining 'cases' using a cut-off consistent with the percentage of cases identified by Achenbach in a community sample (Bor et al., 1997). Using a selected subsample of 76 parents at child age 5 years who completed the full version of the CBCL, the correlation between the full form and short form for total behaviour problems was found to be very high ($r = 0.98$) (Bor et al., 1997). Also at 5 years, children completed the Peabody Picture Vocabulary Test – Revised (PPVT-R), requiring them to indicate which one of four illustrations best represented a word expressed verbally by the examiner, resulting in a score measuring the subjects verbal ability (Jongsma, 1982). The PPVT-R has been validated against other standardised intelligence tests used on children (Childers et al., 1994; Dunn, 1981; Johnson et al., 1993).

2.5. Confounders

Maternal age, parity and level of education (incomplete high school/completed high school/undertaken tertiary education) were collected prenatally. In addition, mothers were asked how often and how much alcohol they consumed since becoming pregnant (none/light/moderate/heavy), and offspring gender was recorded at birth. At the five year follow-up mothers again completed the Social Readjustment Rating Scale (Holmes and Rahe, 1967) (past six months) to give a stressful life events concurrent to child behaviour problems.

2.6. Statistical analysis

We explored the factor structure of the psychotic experiences with Exploratory Factor Analysis (EFA) using the Mplus version 6 default geomin rotation which is an oblique rotation method and is recommended in cases where a factor indicator may have a substantial loading on more than one factor (Browne, 2001; Muthén, 1998–2010), and using the Mplus weighted least squares with mean and variance adjustment (WLSMV) estimator which is appropriate for categorical data and shown to yield accurate test statistics, parameter estimates and standard errors under non-normal latent response distributions (Byrne, 2012). Next, we used Confirmatory Factor Analyses (CFA) guided by the EFA results, to test a range of structures including a single factor, multiple factors (correlated), and second-order and bifactor models (Chen et al., 2006). Model fit was assessed using the Root Mean Square Error of Approximation (RMSEA), the Comparative Fit Index (CFI), and the Tucker–Lewis Index (TLI), for which adequate fit is indicated by RMSEA < 0.06, CFI ≥ 0.95 and TLI ≥ 0.95 (Hu and Bentler, 1998). We took a systematic approach to our structural equation modelling, firstly assessing each variable for inclusion using univariate analysis. The risk factors were included in the full structural model only if they predicted the outcome in univariate analyses, while confounders were included *a priori*. In addition, we tested for the interaction of [(i) prenatal stressful life events × behaviour problems; (ii) prenatal stressful life events × cognitive ability], on the outcome. We used the continuous score of behaviour problems and cognitive ability in the interaction terms.

The final SEM was then constructed as follows: (i) temporally appropriate pathways were allowed between the risk factors, and the outcome was regressed on all of these factors; (ii) non-significant pathways were removed; (iii) every variable in the model was regressed on all confounding variables; (iv) non-significant pathways were removed before calculation of indirect parameter estimates of the effect of prenatal stressful life events on the outcome via behaviour problems. We used bootstrapping [1000 samples] to obtain bias corrected bootstrapped 95% confidence limits for the unstandardised indirect parameter estimates, which is preferable to the delta method (details of both methods can be found in MacKinnon et al. (2007)), resulting in the final model (estimates are probit regression parameters).

We conducted a supplementary analysis to assess the psychopathological significance of our psychotic experiences factors by using them to predict common lifetime DSM-IV mental disorders also derived from the CIDI at age 21. To address loss to follow-up, we used multivariate logistic regression in Stata v.12 to compare those who had been lost to follow-up with those used in the final analysis on a number of baseline variables to assess attrition bias on our results. In addition, from the multivariate logistic regression model we produced weights representing the inverse probability of each participant being included in the study. The final analysis was then replicated using these weights. We used inverse probability weighting instead of multiple imputation because missingness was likely to be associated with our outcome in addition to the risk factors (Lee and Carlin, 2012).

3. Results

The prevalence of individual life time delusions and hallucinations was very low in our sample, ranging between 1.1-3.7% and 1.3–8.8% respectively (see Supplementary Table 1), and 624 (24%) individuals had at least one psychotic symptom. This low prevalence reflects our method of psychotic experiences ascertainment by which positive responses were probed for truly psychotic content. In all, 36 people received a DSM-IV diagnosis of any psychotic disorder, including four with schizophrenia, four with delusional disorder, four with schizophreniform and 24 with brief psychotic disorder. The results of the measurement model revealed the positive experiences of psychosis were best represented by a bifactor model (shown in Fig. 1) which included a general psychosis factor, onto which all indicators loaded, and two group specific factors defined by paranoia/reference and thought interference (see supplementary section for a comprehensive summary).

Table 1 shows the results of the univariate analyses in which the risk factors and confounders were regressed on the three factors of the bifactor model. Of the risk factors, prenatal stressful life events and smoking, in addition to total behaviour problems and PPVT-R at age 5 years predicted the general factors of positive experiences of psychosis. Maternal stressful life events reported at child age 5 years was not associated with psychotic experiences. Of the confounding factors, gender and maternal education predicted psychotic experiences. Thus, all non-significant risk factors were dropped (in addition to PPVT-R which) from further analysis, while the confounders were retained, as according to the approach outlined in the methods section.

We found no statistical evidence for interaction [(i) prenatal stressful life events × behaviour problems $p = 0.863$; (ii) prenatal stressful life events × cognitive ability $p = 0.805$]. Risk factors not found to predict psychotic experiences including cognitive ability and maternal stressful life events during childhood were excluded from further analysis and the group specific factors of paranoia/reference and thought interference were not predicted.

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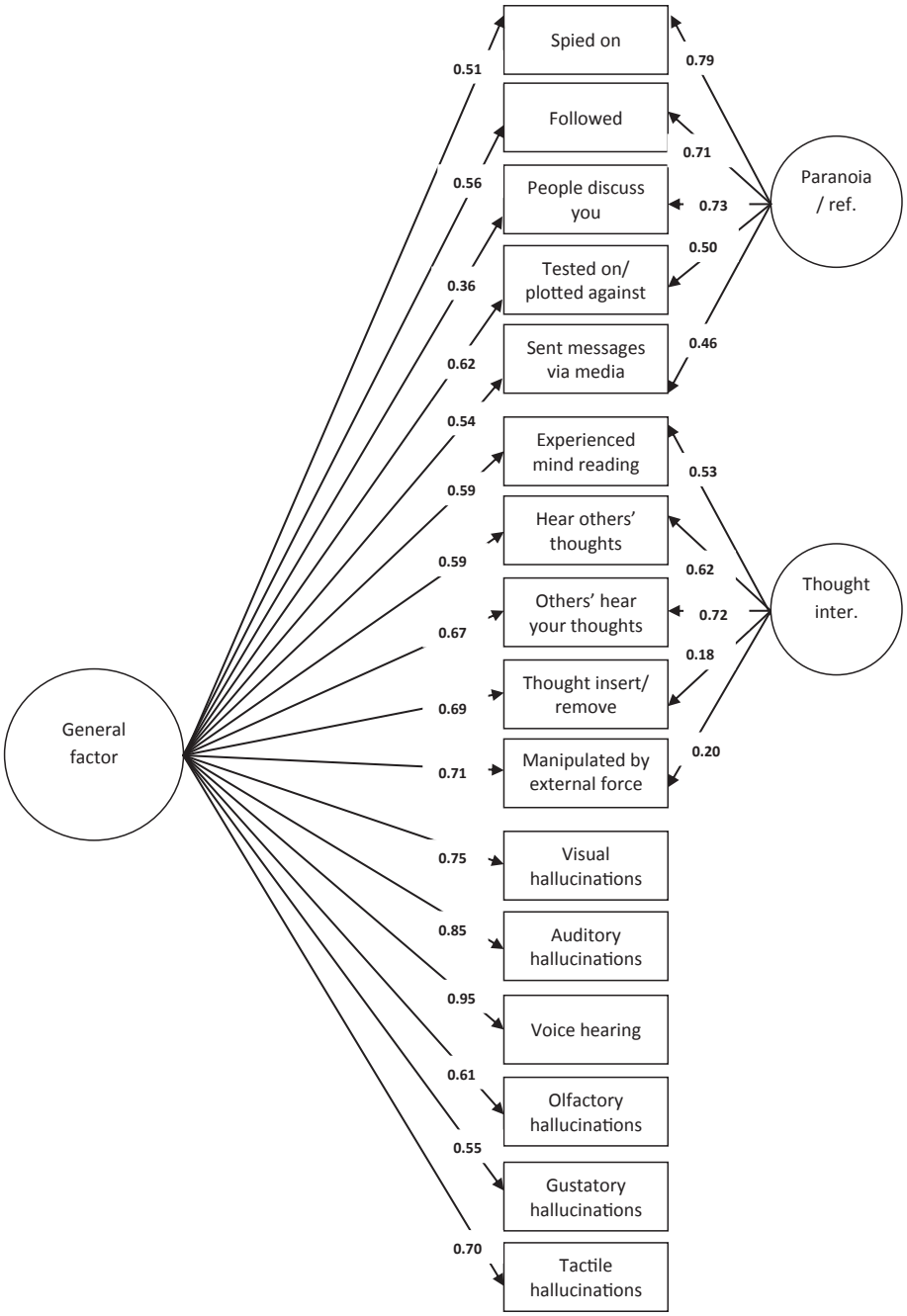

Fig. 1. Bifactor model of lifetime positive psychotic experiences at age 21 years (standardised factor loadings).

The final model was then constructed following the steps given in the methods. Prenatal stressful life events did not predict psychotic experiences directly, but indirectly via childhood behaviour problems, producing an indirect effect via both the delta and bias corrected bootstrapping methods. In addition, after adjustment for confounders prenatal smoking no longer predicted psychotic experiences, due mostly to the addition of maternal education (see Table 2 and Fig. 2).

Despite maternal stressful life events at child age 5 years not predicting the outcome in univariate analysis, we carried out a sensitivity analysis including it in the final model to be more certain the indirect effect was not confounded by this factor. We found stressful life events at 5 years did not predict the outcome and did not substantively change the direct or indirect parameters of interest (results available from corresponding author). The supplementary analysis revealed that the general factor of psychotic experiences strongly predicted all DSM-IV disorders tested (Table 3), the paranoia/reference factor predicted social phobia, while the thought interference factor did not predict any disorders.

Results from the attrition analysis showed that mothers who were lost to follow-up were more likely to be younger, have previous children, less likely to have completed high school, more likely to smoke and to drink at low levels. In addition, mothers lost to follow-up had a small increase in the number of stressful life events experienced during pregnancy. When we replicated our analysis using inverse probability weights, as a method to determine if our results had been biased by attrition, we found the

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Table 1
Univariate associations between the predictors, mediators and confounders with bifactor of psychotic experiences.

Risk factors	*n*	General psychotic experiences				Experiences of paranoia and reference				Experiences of thought interference			
Prenatal/perinatal		USPE	SE	*p*-value	SPE	USPE	SE	*p*-value	SPE	USPE	SE	*p*-value	SPE
Stressful life events (prenatal)	2542	0.06	0.03	**0.030**	**0.08**	0.04	0.05	0.921	0.05	−0.03	0.05	0.548	−0.03
Smoking (prenatal)	2533	0.14	0.05	**0.008**	**0.09**	0.02	0.10	0.871	0.01	−0.03	0.09	0.722	−0.03
Maternal anxiety (prenatal)	2519	0.02	0.02	0.481	0.02	−0.01	0.04	0.733	−0.02	−0.02	0.04	0.648	−0.03
Maternal depression (prenatal)	2523	0.00	0.03	0.895	−0.01	0.03	0.05	0.528	0.03	0.02	0.05	0.770	0.02
Pre-eclampsia (birth)	2558	−0.06	0.12	0.606	−0.06	0.00	0.23	0.987	0.00	0.16	0.22	0.473	0.16
Bwt continuous (birth)	2558	−0.03	0.03	0.410	−0.03	0.01	0.06	0.921	0.01	−0.05	0.07	0.471	−0.05
Bwt ≤10 percentile (birth)	2558	0.18	0.12	0.117	0.18	−0.08	0.22	0.718	−0.08	−0.10	0.02	0.654	−0.10
Apgar score <7 (birth)	2431	0.04	0.10	0.681	0.04	0.18	0.15	0.230	0.18	−0.07	0.16	0.657	−0.07
Forced induction of labour (birth)	2502	0.01	0.07	0.909	0.01	−0.18	0.13	0.161	−0.18	0.05	0.12	0.674	0.05
Baby specialist medical attent. (birth)	2523	0.06	0.05	0.234	0.04	−0.11	0.08	0.199	−0.07	−0.11	0.09	0.239	−0.07
Negative life events (5 yrs)	2160	0.05	0.03	0.063	0.07	0.03	0.05	0.580	0.04	−0.04	0.05	0.440	−0.05
Total behaviour problems (5 yrs)	2306	0.33	0.11	**0.003**	**0.10**	0.04	0.19	0.853	0.01	−0.34	0.21	0.100	−0.11
PPVT-R continuous score (5 yrs)	1953	−0.01	0.00	**0.049**	**−0.08**	0.00	0.01	0.367	0.06	0.00	0.01	0.539	0.044
PPVT-R dichotomised (lowest 10%) (5 yrs)	1953	0.07	0.12	0.539	0.07	0.06	0.19	0.287	0.06	−0.251	0.283	0.375	−0.25
Confounders													
Maternal age (prenatal)	2558	−0.01	0.01	0.237	−0.04	0.00	0.01	0.836	−0.01	0.00	0.01	0.836	−0.01
Parity (prenatal)	2558	0.01	0.03	0.669	0.02	−0.02	0.05	0.744	−0.02	−0.09	0.06	0.132	−0.11
Maternal education (prenatal)	2540	0.16	0.06	**0.004**	**0.10**	−0.01	0.09	0.889	−0.01	−0.28	0.11	0.010	−0.164
Prenatal alcohol (prenatal)	2540	0.02	0.05	0.712	0.01	−0.04	0.08	0.631	−0.02	0.05	0.09	0.590	0.03
Offspring gender	2558	0.23	0.07	**0.001**	**0.23**	−0.34	0.13	0.006	−0.34	−0.30	0.12	0.12	−0.30

Note: Estimates presented as Unstandardised Parameter Estimates (USPE), Standard Errors (SE) and *p*-values, and Standardised Parameter Estimates (SPE).

results were virtually the same as those presented here (see Supplementary Tables 2 and 3).

4. Discussion

Using data from a prospective pre-birth cohort study, we found statistical evidence for mediation, suggesting that premorbid behavioural problems in childhood represent the early neuro-developmental sequelae of exposure to prenatal stressful life events, later resulting in a greater risk of psychotic experiences as the subject ages. This interpretation is consistent with previous research into prenatal infections (Brown et al., 2001; Ellman et al., 2009). On the other hand, we found that prenatal stressful life events and premorbid behavioural problems were not related to later psychosis experiences in a manner consistent with the theory that abnormal development represents the early manifestation of a genetic susceptibility to schizophrenia, moderating the risk of prenatal stress. This does not support findings from a previous study where the risk of schizophrenia due to obstetric complications was moderated by delays in early motor development (Clarke et al., 2011). Support for mediation, along with our interpretation of the significance of developmental abnormalities to psychotic illness, is found in animal studies which inherently control for genetic variability and find that the increased post-adolescent schizophrenia-like behaviour in rats exposed to prenatal stress is preceded by cognitive, behaviour and loco-motor abnormalities (Meyer and Feldon, 2010). In summary, we elucidated an important factor in the pathway from prenatal stress to psychotic experiences, thus providing novel evidence in support of the neuro-developmental model of schizophrenia and related disorders.

An important consideration of our results is that child behaviour problems predicted psychosis experiences regardless of the inclusion of prenatal stressful life events in our model. A previous MUSP study found that behaviour problems at age 5 and 14 years predicted an increased risk of delusions at age 21 (Scott et al., 2009), measured using the self-reported Peter's Delusional Inventory (PDI) (Peters et al., 2004). Thus it may be that the risk of psychotic experiences due to behaviour problems, not explained by previous environmental exposures, is indicative of genetic susceptibility (Cannon et al., 2002a). It also remains possible that additional early-life environmental exposures are responsible for the abnormalities which precede schizophrenia, as has been found for prenatal infections (Brown et al., 2001; Ellman et al., 2009), but not for obstetric complications (Clarke et al., 2011; Bearden et al., 2000). Importantly, the R-square of the final model revealed the combination of behaviour problems and gender explained only 5% of the variance of the outcome, meaning other environmental or genetic factors need to be identified to better explain the occurrence of psychotic experiences.

Table 2
Structural equation model showing weighted least squares (WLSMV) estimates of the direct and indirect effect of prenatal maternal stress and smoking on offspring positive experiences of psychosis at age 21 ($n = 2227$).

Outcome/mediator/ prenatal risk	Predictor	USPE	SE	*p*-value	SPE
Direct effects					
Psychotic experiences (21 yrs)	Total behaviour problems (5 yrs)	0.20	0.06	<0.001	0.19
Total behaviour problems (5 yrs)	Stressful life events (prenatal)	0.16	0.03	<0.001	0.19
	Smoking (prenatal)	0.25	0.06	<0.001	0.15
Stressful life events (prenatal)	Parity	0.08	0.03	0.005	0.07
	Maternal age (prenatal)	−0.04	0.01	<0.001	−0.14
Smoking (prenatal)	Parity	0.03	0.01	0.018	0.06
	Maternal age (prenatal)	−0.02	0.00	<0.001	−0.16
	Maternal education (prenatal)	0.16	0.02	<0.001	0.16
	Maternal alcohol (prenatal)	0.16	0.02	<0.001	0.15
Indirect effects					
Psychotic experiences (21 yrs)	Stressful life events (prenatal) via behaviour problems (5 yrs)	0.03	0.01	0.003	0.04

Note: Estimates presented as Unstandardised Parameter Estimates (USPE), Standard Errors (SE) and *p*-values, and Standardised Parameter Estimates (SPE).
The bias corrected bootstrapping 95% confidence limits support the unstandardised indirect parameter estimates in the table [prenatal stressful life events USPE = 0.03 (0.01, 0.07)].
Fit indices: CFI = 0.99; TLI = 0.98; RMSEA = 0.011; chi-square = 273.90; D.*F* = 212; *p*-value = 0.003.

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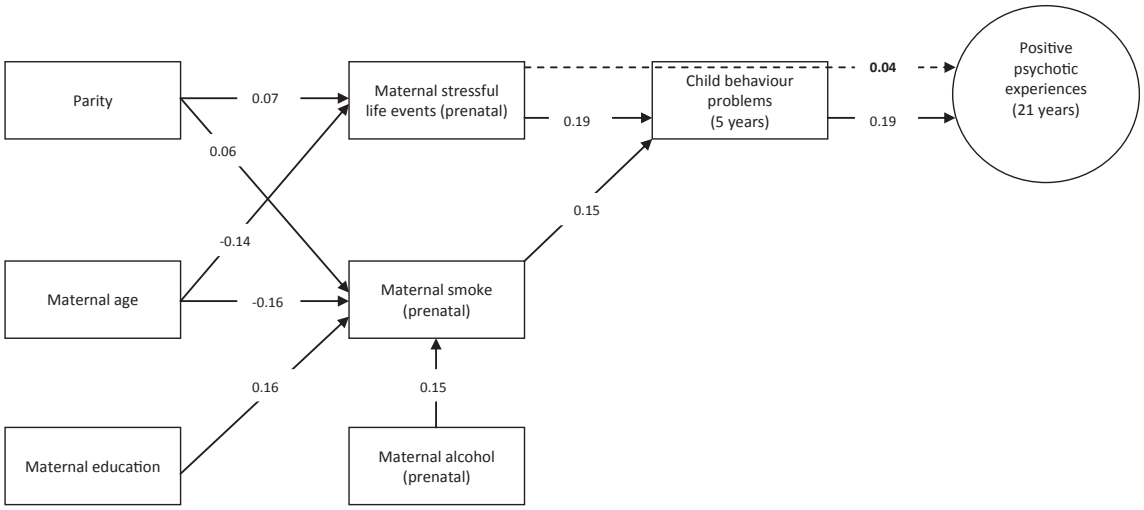

Fig. 2. Structural equation model showing the effects of prenatal maternal stressful life events and smoking, and child behaviour problems on positive psychotic experiences in offspring at 21 years ($n = 2227$). Showing standardised parameter estimates (all estimates are significant at $p < 0.05$ – see Table 3 for standard errors and p-values). The outcome is the general factor from the bifactor model. The dashed line represents the indirect estimates of prenatal stressful life events > child behaviour problems > psychotic experiences. Indirect estimates bolded.

Animal models indicate that increased maternal stress hormones, produced in response to prenatal stressors, cross the placenta and result in permanent changes in regions of the developing fetal brain associated with schizophrenia (King et al., 2010), and result in schizophrenia-like behaviours in adult rats which are preceded by several abnormalities detailed earlier (Meyer and Feldon, 2010). However, the majority of early environmental exposures and premorbid developmental abnormalities which have been studied are non-specific risk factors for a range of psychiatric outcomes in adults (Meyer and Feldon, 2010), suggesting that common pathways to general psychopathology may intersect with specific risk factors to produce particular psychiatric outcomes (Cannon et al., 2002a). A case-control study concluded that additional unknown genetic and/or environmental factors are necessary to make the prenatal brain susceptible to the increased premorbid cognitive abnormalities and psychotic disorders caused by prenatal influenza, as influenza did not influence cognitive ability in control subjects (Ellman et al., 2009). Genetic factors clearly play a role, and studies using a family history of schizophrenia as a proxy of genetic susceptibility find this factor is a necessary condition for the increased risk of schizophrenia associated with selected prenatal and perinatal risk factors (Clarke et al., 2009; Keskinen et al., 2013; Cannon et al., 2002b). However, the importance of environmental exposures is supported by the aforementioned animal studies which inherently control for genetic variation (Meyer and Feldon, 2010), and human studies which show that early environmental risks can also interact with one another to increase the risk of psychotic disorders (Fineberg et al., 2013).

Our study had a number of strengths. A number of aspects of our design were intended to facilitate a causal interpretation insofar as is possible for non-experimental studies. These aspects included temporally appropriate relationships among prospectively measured factors, whose relationships have theoretical and empirical support, and strong estimates, including an indirect pathway based on the latest mediation methodology (MacKinnon et al., 2007). The direct effect of behaviour problems led to a change of 0.20 SD units of the outcome, while the indirect effect of prenatal life events led to a change of 0.03 SD units of the outcome indirectly via behaviour problems. Thus, roughly 13% of the effect of behaviour problems on the outcome was contributed by the indirect effect from prenatal life events. Our findings remained robust after adjustment for a range of confounding factors, including prenatal and perinatal risk factors and maternal stressful life events concurrent to child behaviour at 5 years. Finally, we extend the findings of a recent study which found that prenatal stressful life events did not predict psychotic experiences in children aged 12 years after accounting for prenatal depression and anxiety (Dorrington et al., 2013). These factors did not predict the outcome in our results, and the inconsistencies in our findings may reflect the different ages of the samples. Evidence shows that psychotic experiences are less transitory and take on increasing clinical significance as individuals age (Kelleher et al., 2012), and thus the relationship between prenatal stress and psychotic

Table 3
Univariate associations between the general and two specific factors of positive psychotic experiences with DSM-IV lifetime disorders at age 21 years [Parameter estimates are probit regressions using WLSMV estimation] ($n = 2558$).

Psychosis factors	MDD			GAD			Mania			Social phobia			PTSD		
	USPE	SE	p-value	USPE	SE	p-value	USPE	SE	p-value	USPE	SE	p-value	USPE	SE	p-value
General factor	0.46	0.04	<0.001	0.43	0.06	<0.001	0.45	0.07	<0.001	0.33	0.05	<0.001	0.36	0.06	<0.001
Paranoia/reference	0.02	0.08	0.829	0.00	0.11	0.963	0.18	0.11	0.087	0.20	0.09	0.029	0.05	0.11	0.629
Thought interference	−0.04	0.07	0.578	−0.17	0.11	0.129	−0.13	0.16	0.418	0.01	0.09	0.934	−0.02	0.09	0.825

Note: Major Depressive Disorders (MDD), Generalised Anxiety Disorders (GAD), Post-traumatic Stress Disorders (PTSD).
Estimates presented as Unstandardised Parameter Estimates (USPE), Standard Errors (SE) and p-values; Standardised Parameter Estimates (SPE) are not shown because they are equivalent to USPE.

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experiences may become more evident in early adulthood than in childhood.

Our outcome measured the dimensional model of positive experiences of psychosis with an increased level of specification compared with previous risk factor studies which have predicted psychotic experiences. Firstly, epidemiological investigations into psychotic experiences have mostly relied on measurements ascertained via self-report or structured interview. These methods overestimate the prevalence of psychotic experiences in the population and underestimate their importance by not probing positive responses to confirm their psychotic nature (Zammit et al., 2013). We used psychotic experiences derived from a semi-structured interview, and as expected the majority of positive responses were in fact deemed non-psychotic after further probing. Further, 1.4% of our sample was diagnosed with any DSM-IV psychotic disorder, which is in line with prevalence estimates calculated in reviews (Jablensky, 2000; Saha et al., 2005). Secondly, the psychosis continuum is most often operationalised as a simple count of number of experiences (Van Os et al., 2009), which ignores the complicated structure of the psychosis continuum. We used structural equation modelling to properly specify the multidimensional phenotype of psychosis, distinguishing between core symptomatic expression and unrelated variance. In doing so we found a structure closely representing the three principle dimensions of positive experiences of psychosis identified previously (Wigman et al., 2012, 2011), and then imposed a general construct across the three highly correlated psychotic subdimensions (Reininghaus et al., 2013). Lastly, our general factor of positive experiences of psychosis was found to have strong psychopathological significance, and was strongly related to non-psychotic DSM-IV disorders also measured at 21 years.

Our study also had a number of limitations. Firstly, as the stressful life events may have occurred at any stage over the last 6 months of gestation, we were unable to provide information with regard to what period during pregnancy may be the most sensitive for an increased risk of later psychotic experiences. Recent studies find that stressful life events are most predictive of schizophrenia and affective disorders if exposure occurs in the first and second trimesters (Khashan et al., 2008, 2011; Kleinhaus et al., 2013), while exposure in the third trimester may predict autism disorders (Class et al., 2013). Thus had we exposure information during trimester 1 we may have found a stronger relationship. Further, if we had been able to measure events occurring across the entire pregnancy and define the trimester in which the stressful life events had occurred, we may have found a more robust association. Secondly, we argued that the premorbid behavioural abnormalities which mediated the relationship between prenatal stress and later psychotic experiences represented pre-schizophrenia sequelae due to the environmental insult. However, as findings show premorbid behaviour to be present in the unaffected siblings of individuals with schizophrenia (Bearden et al., 2000), and much of the premorbid abnormalities are yet to be explained by preceding environmental exposures (Cannon et al., 2002a), genetic factors related to schizophrenia risk are likely to play a crucial role in the indirect relationship we found. That we could explore neither molecular nor proxy genetic factors is a major limitation in need of redress by future studies. Further, additional genetic and environmental factors not included in our study are needed to explain how non-specific risk factors (such as prenatal stressful life events and childhood behaviour problems) lead to psychotic illness instead leading to other psychiatric outcomes. Thirdly, unlike previous research which studied truly independent stressful events (Khashan et al., 2008; Van Os and Selten, 1998; Selten et al., 1999; Malaspina et al., 2008), we used every day stressful life events which although measured objectively may be partly influenced by maternal or paternal personality and temperament. As these factors are partly heritable and may impact offspring behaviour and psychotic experiences, this represents another pathway by which genetic factors may have confounded the relationship. Finally, our cohort was subject to considerable attrition, which was related to prenatal stressful life events. Despite this, results from our inverse probability analysis suggested attrition did not substantively change any parameter estimates in our model.

In conclusion, our findings suggest that the impact of prenatal stressful life events on later psychotic experiences is mediated via a broad measure of behavioural problems at age five. As we controlled for a number of important confounders and used prospective measures of risks and outcome, our results suggest the consequences of exposure to prenatal stress may appear early, manifesting as general behavioural problems, before resulting in increased risk of psychotic experiences. As both prenatal stressful life events and child behaviour problems are non-specific risks for a range of psychiatric disorders in adulthood, further studies should investigate what other conditions are necessary along this pathway to ultimately result in psychotic experiences. Lastly, further investigation into the clinical significance of psychotic experiences and how they relate to non-psychotic psychiatric disorders is necessary.

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Contributors

Authorship: KB devised the hypothesis, study design, conducted initial analysis and wrote the first draft of the manuscript. GMW provided statistical consultation and contributed to drafting the final version of the manuscript. JMN contributed to MUSP study design data collection and writing. JS and RA contributed to data interpretation and writing of the manuscript. All authors provided critical input and approved the final version of the manuscript.

Conflict of interest

All authors declare no conflicts of interest.

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Ethical Standards: Informed consent from all participants was gained, all data was coded for confidentiality and ethics was approved for the cohort by the institution and funding body.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jpsychires.2014.08.001.

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Maternal prenatal infection, early susceptibility to illness and adult psychotic symptoms

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Study purpose: This study used a similar methodology to that previous to investigate another potential mediator of the risk of offspring psychotic experiences. It tested whether the association between prenatal maternal infection and later offspring psychotic experiences represented a direct relationship or was mediated via infant illness susceptibility.

Supplementary material: Some information relevant to this study (i.e., attrition, IPW and MMI analyses) was published online in a supplementary section only and can be accessed at: http://www.sciencedirect.com/science/article/pii/S0920996414001716

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Maternal prenatal infection, early susceptibility to illness and adult psychotic experiences: A birth cohort study

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ABSTRACT

Background: Existing evidence has established that maternal infection during pregnancy and illness during early life are associated with later schizophrenia. No research has examined how the combination of these prenatal and postnatal exposures is linked to an increased risk to later schizophrenia and psychotic disorders.
Methods: Participants from the Mater University Study of Pregnancy (MUSP), an Australian based, pre-birth cohort study were examined for lifetime DSM-IV positive psychotic experiences at 21 years by a semi-structured interview. Structural equation modelling was used to derive a general factor of psychotic experiences at age 21. Next, we undertook a number of separate analyses to investigate how prenatal infections and infant illness susceptibility are related to positive psychotic experiences in early adulthood, allowing for tests of moderation and mediation between the two risk factors.
Results: After adjustment for important confounders, infant illness susceptibility was found to play a mediating role in the association between prenatal vaginal infection and later psychotic experiences. Whereby, infant illness susceptibility showed a direct association with psychotic experiences, while prenatal vaginal infection indirectly predicted psychotic experiences via infant illness susceptibility.
Conclusion: Our findings suggest that illness susceptibility in early infancy may be central to the relationship between prenatal vaginal infection and later psychotic experiences. Further research is needed to establish the mechanisms that link these prenatal and postnatal exposures with psychotic illness in later life.

1. Introduction

The neurodevelopmental model of schizophrenia suggests factors impacting during early neurodevelopment may influence the risk of later schizophrenia (Rapoport et al., 2012). Maternal prenatal infection is one such factor (Brown and Derkits, 2010), with genital/reproductive infection being one of the most prevalent groups of prenatal infections to be associated with schizophrenia (Brown et al., 2011), possibly contributing to 6% of schizophrenia cases (Brown and Derkits, 2010). A recent meta-analysis examining the effects of a range of prenatal infections on schizophrenia concluded that while existing evidence supports the association, there is a need for more sophisticated statistical models with the ability to properly account for mediating factors (Khandaker et al., 2013b). Another line of investigation has also found that early postnatal development may be a sensitive period during which a range of illnesses including infections (Khandaker et al., 2012) and atopic disorders (Pedersen et al., 2012; Khandaker et al., 2013a) increase the risk of later schizophrenia (Khandaker et al., 2012). However, research has not tested for interrelationships among these two exposures with schizophrenia or related disorders.

Aside from the possibility that prenatal infection and infant illness susceptibility may represent independent risk factors for schizophrenia, there are several ways in which the relationship between the two exposures may result in an increased risk of schizophrenia. Firstly, exposure to prenatal infection and infant illness susceptibility may have a cumulative effect on schizophrenia, whereas exposure to either but not both may not be sufficient to predict schizophrenia. A 'moderating' effect such as this could be considered consistent with the 'two hits' hypothesis of schizophrenia development, which views prenatal infection as a 'disease primer' leaving an individual susceptible to schizophrenia in the event of further environmental insults (Meyer, 2013).

Secondly, it is possible that prenatal infection indirectly increases the risk of adult schizophrenia via infant illness susceptibility. Such a 'mediating' effect may indicate that maternal prenatal infection was

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transmitted to the fetus (Brown and Derkits, 2010) resulting in persistent or recurrent postnatal illness (Remington et al., 2010) which increases schizophrenia risk (Khandaker et al., 2012). Thirdly, it is possible that when testing for the effects of both exposures, only one will predict the outcome, revealing the period in which the developing brain is most sensitive to the risk of schizophrenia posed by exposure to illness and infection. Lastly, other potentially 'causal' risk factors of later schizophrenia may explain the effect attributed to either primary exposure. Prenatal smoking, pre-eclampsia, birth weight, preterm birth, induced labour, and fetal hypoxia appear to be associated with an increased risk of offspring schizophrenia and psychotic disorders (Cannon et al., 2002; Canon et al., 2002; Zammit et al., 2009; Nosarti et al., 2012; Eide et al., 2013; Stathopoulou et al., 2013), and have been linked to the exposures (King et al., 2010).

Lastly, there is agreement that the positive psychotic experiences, which are central to the diagnosis of schizophrenia and other psychotic disorders, exist as a dimensional phenotype (Ahmed et al., 2012; Subramaniam et al., 2013; Zammit et al., 2013) and represent a 'trait diathesis' which in extreme cases converts to schizophrenia and other psychotic diagnoses (Rapoport et al., 2012). Empirically, subthreshold psychotic experiences are influenced by similar risk factors which predict schizophrenia (van et al., 2009; Linscott and van, 2010), and are found to predict future psychosis (Fisher et al., 2013), which may necessitate clinical care (Yung et al., 2012). Previous studies based on the ALSPAC found a range of prenatal and perinatal risk factors, including prenatal infection, predicted an increased risk of psychotic experiences in children (Thomas et al., 2009; Zammit et al., 2009; Dorrington et al., 2013). In this study, we extend these findings by using structural equation modelling to assess how key prenatal and postnatal risk factors associate to predict the more serious psychotic experiences of later developmental stages (Kelleher et al., 2012). Specifically, we examine whether the impact of infant illness susceptibility on psychotic experiences in early adulthood is moderated by prenatal vaginal infection, or if the impact of prenatal vaginal infection on psychotic experiences is mediated via infant illness susceptibility.

2. Methods

2.1. Participants

Participants came from the Mater University Study of Pregnancy (MUSP), a prospective pre-birth cohort study following mothers and their children for over 20 years. A total of 7,223 mothers attending their first clinic visit at Brisbane's Mater Misericordiae Hospital were recruited between 1981 and 1984, with subsequent follow-ups at birth, and child age 6 months, and 5, 14 and 21 years, further information found elsewhere (Najman et al., 2005). At 21 years 2,558 offspring completed the Composite International Diagnostic Interview (CIDI-Auto 2.1) (World Health Organization, 1997), providing the sample to examine the factor structure of psychosis. The final model included participants with values on all variables of interest ($n = 2{,}329$).

2.2. Positive psychotic experiences

At the 21 year follow-up the lifetime version of the CIDI-Auto (World Health Organization, 1997) was administered by trained interviewers, including items assessing positive psychotic experiences (15 delusions and 6 hallucinations). Affirmative responses to delusions and hallucinations were probed to be surer the experience was psychotic. As the prevalence of experiences was low, it was necessary to combine three pairs of 'like' delusions (1) tested on/plotted against (being secretly tested on/someone was plotting to hurt you), (2) thought removal/insertion (thoughts were inserted into your mind/thoughts were taken from your mind), and (3) manipulated by external force (felt under the control of an external force/felt strange forces working on you), and exclude two delusions [(i) convinced someone you never met was in love with you; (ii) convinced your partner was cheating on you], resulting in a total of 16 psychotic experiences.

2.3. Risk factors

Vaginal infection was ascertained at birth when mothers reported if they had experienced vaginal infection/discharge over pregnancy (did not happen/ minor problem/ moderate problem/ major problem). Infant illness susceptibility was constructed as a single latent variable capturing the 'co-occurrence' of two indicator variables reported by mothers at infant age 6 months: (1) how many times medical attention had been sought for the infant (0/1/2/3–4/5+), and (2) four questions regarding the frequency (never/rarely/monthly/weekly/often) of health problems possibly resulting from infection (vomiting, diarrhoea/constipation, skin rashes, cold/cough/runny nose), which were summed.

Additional prenatal and perinatal risk factors which prior work indicate may play a causal role in the main hypothesis were ascertained at birth, including Apgar score (<7 at 1 minute), forced induction of labour, pre-eclampsia, and birth weight z-score adjusted for gestational age and gender (Betts et al., 2013), and if the baby required "specialist medical care" after delivery (did not happen/ minor problem/ moderate problem/ major problem). In addition, at the first clinic visit pregnant mothers were asked how many cigarettes they had smoked in the last week (none/1–19/20+).

2.4. Potential confounders

At the first clinic visit pregnant mothers were asked how often and how much alcohol they consumed since becoming pregnant (none/light/moderate/heavy). Maternal age, parity and level of education (incomplete high school/complete high school/undertaken tertiary education) were also collected at this time, while baby gender was taken at birth.

2.5. Statistical analysis

To examine the factor structure of the psychotic experiences we conducted Exploratory Factor Analysis (EFA) using the WLSMV estimator available in Mplus version 6, capable of handling the non-normality associated with categorical data. We then used the EFA results to undertake a number of Confirmatory Factor Analyses (CFA) (Chen et al., 2006). Model fit was assessed using the Root Mean Square Error of Approximation (RMSEA), the Comparative Fit Index (CFI), and the Tucker-Lewis Index (TLI), for which adequate fit is indicated by RMSEA < 0.06, CFI ≥ 0.95 and TLI ≥ 0.95 (Hu and Bentler, 1998).

Next we constructed the path analysis (regression) model. To avoid complicated model building strategies which may result from the inclusion of so many variables and pathways, we assessed each variable for inclusion using univariate analysis. Predictor variables were divided into risk factors and confounders (Table 2). Risk factors were included in the path analysis only if they predicted the outcome in univariate analysis, while confounders were included *a priori*. The remaining variables were then entered into the path analysis, connected by temporally appropriate pathways, before removing non-significant pathways by a systematic process (see supplementary text 1). Lastly, two separate analyses assessed whether: (1) the effect of infant illness susceptibility on psychotic experiences was moderated by prenatal vaginal infection; or (2) the effect of prenatal vaginal infection on psychotic experiences was mediated via infant illness susceptibility. A description of the statistical tests of moderation and mediation can be found in supplementary text 2.

We conducted a supplementary analysis to assess the psychopathological significance of our psychotic experiences factors by using them to predict common lifetime DSM-IV mental disorders also derived from the CIDI at age 21. Finally, we used multivariate logistic regression in Stata v.12 to compare those who had been lost to follow-up with

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those used in the final analysis on a number of baseline variables to assess attrition bias on our results. Next, we produced weights representing the inverse probability of each participant being included in the study from the multivariate logistic regression model. The final analysis was then replicated using these weights.

3. Results

3.1. Measurement model

The prevalence of life time delusions and hallucinations are shown in Table 1, and 36 people received a DSM-IV diagnosis of any psychotic disorder (four with schizophrenia, four with delusional disorder, four with schizophreniform and 24 with brief psychotic disorder). Table 1 shows the positive psychotic experiences were best represented by a bifactor model which included a general psychosis factor, onto which all indicators loaded, and two group specific factors defined by paranoia/reference and thought interference (illustrated in Fig. 1). For comprehensive details of how the bifactor model was arrived at see the supplementary text 3. Importantly, only the general factor was of interest in further analyses.

3.2. Path analysis

Prenatal vaginal infection, prenatal smoking, infant illness susceptibility, maternal education and offspring gender predicted psychotic experiences (Table 2). The path analysis (i.e., the final model) was then constructed. (i) Temporally appropriate pathways were allowed among prenatal infection, prenatal smoking, and infant illness susceptibility, and the outcome was regressed on these risk factors; (ii) the direct effect of prenatal vaginal infection on the outcome was removed as it was non-significant; (iii) all variables in the model (risk factors and outcome) were regressed on all confounders; (iv) all non-significant paths were removed (including the direct effect of prenatal smoking on psychotic experiences).

3.3. Moderation and mediation

There was no evidence of moderation, as the effect of infant illness susceptibility on psychotic experiences was not found to differ significantly between those who were and those who were not exposed to prenatal maternal vaginal infection [(unstandardised parameter estimate among those exposed = 0.15, SE = 0.07, p = 0.039; and those unexposed = 0.17, SE = 0.08, p = 0.044); (Chi-square test for difference testing = 1.028, d.f. = 1, p = 0.311)]. There was evidence for mediation, whereby there was no direct association between prenatal vaginal infection and psychotic experiences. Whereas prenatal vaginal infection predicted psychotic experiences indirectly, via infant illness susceptibility (confirmed using bias corrected bootstrapping) (see Table 3 and Fig. 2). (MacKinnon et al., 2007). See supplementary section for results of the supplementary and attrition analyses.

4. Discussion

We found that maternal prenatal vaginal infection increased the risk of later positive psychotic experiences in offspring via a greater risk of infant illness susceptibility. In addition, infant illness susceptibility during the first 6 months of life strongly predicted later positive psychotic experiences after adjustment for important confounders. Our findings do not support prenatal maternal vaginal infection directly influencing the occurrence of later psychosis symptoms in the absence of other contributing factors. In the case where the second contributing factor is infant illness susceptibility, we found statistical evidence for mediation and not moderation. Thus, rather than being two independent events, by which prenatal infection leaves the infant more vulnerable to the later psychotic experiences associated with early infant illness susceptibility (Khandaker et al., 2012), prenatal infection exerts its influence over later psychotic experiences by its contribution to infant illness susceptibility.

We see two possible explanations for the relationship we found. Infant illness susceptibility, regardless of maternal prenatal vaginal infection status, may increase the risk of later psychotic experiences via a biological pathway. It is possible that inflammatory cytokines

Table 1
Standardised factor loadings (with standard errors) and fit indices for the 1 factor, 3 factor (correlated) and bifactor models of lifetime positive psychotic experiences at 21 years (n = 2,558).

Symptoms (DSM-IV)	Prevalence	1 Factor CFA	3 Factor CFA (correlated factors)			Bifactor model		
	% (n)	Factor 1	Factor 1	Factor 2	Factor 3	General factor	Specific factor 1	Specific factor 2
Delusions (paranoia/reference)								
Spied on	1.8% (46)	0.79 (0.04)	0.89 (0.04)			0.51 (0.07)	0.79 (0.06)	
Followed	2.0% (51)	0.79 (0.04)	0.91 (00.4)			0.56 (0.06)	0.71 (0.06)	
People discussing you	1.4% (37)	0.62 (0.06)	0.73 (0.06)			0.36 (0.08)	0.73 (0.08)	
Tested on/plotted against	1.1% (28)	0.71 (0.05)	0.85 (0.06)			0.62 (0.07)	0.50 (0.08)	
Sent messages via media	1.1% (28)	0.62 (0.06)	0.75 (0.07)			0.54 (0.08)	0.46 (0.11)	
Delusions (thought interference)								
Experienced mind reading	1.6% (40)	0.73 (0.05)		0.79 (0.05)		0.59 (0.07)		0.53 (0.07)
Hear others' thought	3.4% (86)	0.78 (0.03)		0.84 (0.03)		0.59 (0.05)		0.62 (0.07)
Others' hear your thoughts	3.7% (95)	0.85 (0.03)		0.94 (0.03)		0.67 (0.05)		0.72 (0.08)
Thought insertion/removal	1.3% (32)	0.68 (0.06)		0.77 (0.06)		0.69 (0.07)		0.18 (0.09)
Manipulated by external force	1.3% (32)	0.68 (0.06)		0.78 (0.06)		0.71 (0.06)		0.20 (0.10)
Hallucinations								
Visual hallucinations	7.7% (196)	0.70 (0.03)			0.75 (0.03)	0.75 (0.03)		
Auditory hallucinations	4.3% (111)	0.81 (0.03)			0.85 (0.03)	0.85 (0.03)		
Voice hearing	2.2% (55)	0.90 (0.03)			0.95 (0.03)	0.95 (0.03)		
Olfactory hallucinations	4.1% (104)	0.57 (0.05)			0.62 (0.05)	0.61 (0.05)		
Gustatory hallucinations	4.7% (120)	0.51 (0.05)			0.55 (0.05)	0.55 (0.05)		
Tactile hallucination	8.8% (225)	0.65 (0.04)			0.70 (0.04)	0.70 (0.04)		
CFI; TLI		0.92; 0.91		0.99; 0.98			0.99; 0.99	
RMSEA		0.033		0.014			0.010	
Chi-square (free parameters)		395.76 (104)		151.68 (101)			116.94 (94)	

Note: The second-order model (not shown) was considered unsuitable as it had inferior fit (CFI = 0.98; TLI = 0.98, RMSEA = 0.016; chi-2 = 166.33; free parameters = 102) and the first order hallucinations factor had a non-significant residual variance (0.16; p = 0.274).
Parameters were derived using the WLSMV estimator and all factor loadings and factor variances were significant.

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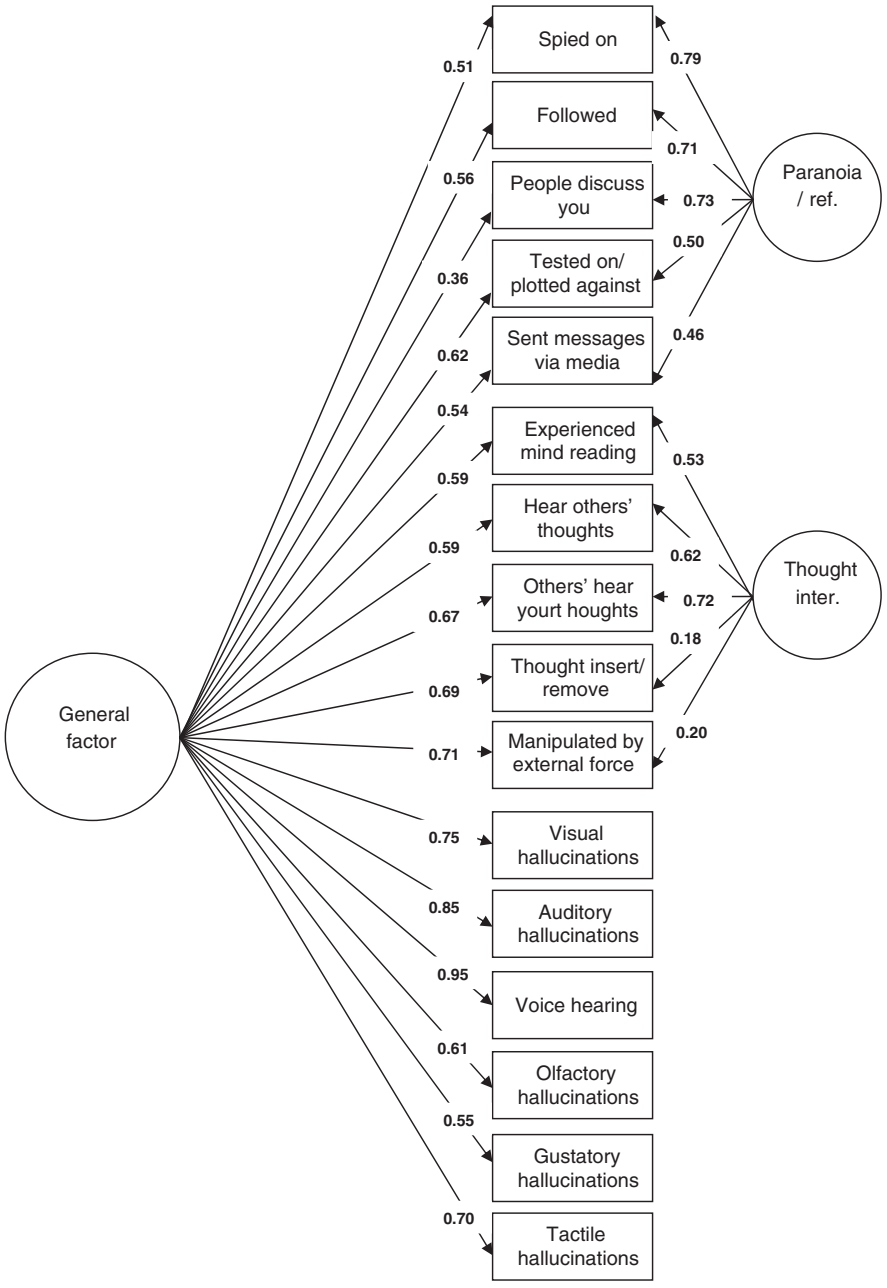

Fig. 1. Bifactor model of lifetime positive psychotic experiences at age 21 years (standardised factor loadings).

produced by the immune system affect the developing brain to increase the risk of later psychotic disorders. This mechanism would explain why psychotic risk is associated with such a broad range of childhood illnesses, including viral and bacterial infections and atopic disorders (Meyer et al., 2009; Khandaker et al., 2012; Pedersen et al., 2012; Khandaker et al., 2013a,b). The absence of a direct effect between prenatal vaginal infection and psychosis symptoms means that the processes by which experimental prenatal infection has been shown to influence *in utero* neurological development in animal models (Meyer, 2013), did not influence later psychotic experiences in our sample. Instead, a small proportion of prenatal infections may have been transmitted to the offspring *in utero*, causing illness susceptibility in the first few months of postnatal life (perhaps via congenital infection), which in turn predicted psychotic experiences via the processes described above (Muller and Schwarz, 2006). Maternal infections may be transmitted to the fetus during gestation via the placenta or contact with the birth canal during delivery, and the resulting infection can manifest in a range of symptoms and developmental abnormalities shortly after birth (Remington et al., 2010). While this possibility could explain our indirect effect, it will need to be confirmed by future research with the capacity to investigate the role of specific congenital infections instead of a broad measure of infant illness susceptibility. Despite this, our results suggest that accounting for early postnatal illness susceptibility is important to the line of research.

Secondly, it is possible that a family liability to infection and psychotic illness could all be influenced by one or more unknown familial genetic and/or lifestyle factors as suggested by a recent study (Nielsen et al., 2013). Mental illness is more common among members of families of lower socioeconomic status and with poorer lifestyles, and these same factors may also drive an increase in infection occurrence (Khandaker et al., 2013b). However, as with studies before us (Khandaker et al., 2013b) we controlled for a range of sociodemographic

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Table 2
Univariate associations between the predictors, mediators and confounders with the general factor of the positive experiences of psychosis.

Risk factors		Psychotic experiences			
	n	USPE	SE	p-Value	SPE
Maternal vaginal infection (prenatal)	2,528	0.10	0.04	**0.009**	**0.09**
Smoking (prenatal)	2,533	0.14	0.05	**0.008**	**0.09**
Pre-eclampsia *(birth)*	2,558	−0.06	0.12	0.606	−0.06
Bwt continuous (birth)	2,558	−0.03	0.03	0.410	−0.03
Bwt ≤10 percentile (birth)	2,558	0.18	0.12	0.117	0.18
Apgar score <7 (birth)	2,431	0.04	0.10	0.681	0.04
Forced induction of labour (birth)	2,502	0.01	0.07	0.909	0.01
Baby specialist medical attent. (birth)	2,523	0.06	0.05	0.234	0.04
*Infant illness suscept. (6 months – latent)**	2,398	0.17	0.08	**0.039**	**0.13**
Confounders					
Maternal age (prenatal)	2,558	−0.01	0.01	0.237	−0.04
Parity (prenatal)	2,558	0.01	0.03	0.669	0.02
Maternal education (prenatal)	2,540	0.16	0.06	**0.004**	**0.10**
Prenatal alcohol (prenatal)	2,540	0.02	0.05	0.712	0.01
Offspring gender – females	2,558	0.23	0.07	**0.001**	**0.23**

Note: Estimates are probit regression parameters presented as unstandardised parameter estimates (USPE), standard errors (SE) and p-values, and standardised parameter estimates (SPE).

* CFI = 0.99, TLI = 0.99, RMSEA = 0.009; infant illness suscept. standardised factor loadings = 0.524, SE = 0.143, p < 0.001; seeking medical care standardised factor loadings = 0.600, SE = 0.165, p < 0.001;

factors and did not find they changed the primary relationship. Alternatively, a shared susceptibility to illness susceptibility and psychotic illness may have a genetic origin, as evidence links several genes associated with schizophrenia risk to those associated with the major histocompatibility complex on chromosome 6, which is responsible for immune system activity (Stefansson et al., 2009).

An additional strength of our paper was the use of psychotic experiences from a semi-structured interview, which by probing positive responses for truly psychotic content do not overestimate the prevalence of psychotic experiences and underestimate their importance (Zammit et al., 2013). Further, using structural equation modelling we identified a factor structure of psychotic experiences closely representing the three principle dimensions of positive symptoms of psychosis identified previously (Wigman et al., 2011, 2012), though we went further by imposing a general construct across the three highly correlated psychotic subdimensions (Reininghaus et al., 2013). Unlike existing longitudinal studies which predict a simple count of psychotic experiences (van et al., 2009), we were able to better identify the multidimensional phenotype of psychosis, distinguishing between the core symptomatic expression of the general factor and the unrelated variance (i.e., group specific factor variance and measurement error). This resulted in a better specified outcome with the consequence of producing more robust associations with risk factors.

Our study also had a number of limitations. Firstly, we were unable to control for a family history of psychotic illness. This factor is however unlikely to explain the relationship we found as only around 15% of people diagnosed with schizophrenia have a family history of schizophrenia (Khandaker et al., 2013b). Secondly, we were unable to assess the type of prenatal vaginal infection and did not include other types of infection, and thus our results may not be generalised to other high prevalence prenatal infections occurring during pregnancy such as influenza. Despite this, evidence suggests a range of prenatal infections may increase the risk of schizophrenia (Brown and Derkits, 2010; Khandaker et al., 2013b), perhaps via a common mechanism (Miller et al., 2013). We were also unable to adjust for the timing of infections during pregnancy, and hence could not confirm whether early pregnancy is a sensitive period for the later development of schizophrenia (Meyer, 2013). Thirdly, our measure of infant illness susceptibility included a range of non-specific symptoms common in infancy and the frequency with which infants required medical attention. While studies support this finding by showing a wide range of specific and non-specific illnesses in childhood are linked with schizophrenia risk (Khandaker et al., 2012, 2013a), future studies able to determine the types of illnesses or infections most strongly related to psychotic disorders are needed. For now, our study highlights common and non-specific experiences of infant illness were related to psychosis symptoms. Fourthly, we only had maternal reports of vaginal infections and experiences of illness in their infant. While this would have resulted in some misclassification, maternal report perhaps included a broader range of vaginal infections and infant illnesses, not limited to those for which medical attention was sought or for which women were specifically tested. Finally, while we encountered considerable loss to follow-up, the exposures were not biased by attrition and the results from our inverse probability analysis replicated our main findings (supplementary section).

In conclusion, this is the first study to consider the role of both prenatal infection and infant illness susceptibility, with the results suggesting infant illness susceptibility may constitute an important and previously overlooked factor in the relationship between prenatal infection and later psychotic illness. Further studies are needed to examine how psychotic experiences result from prenatal infection and infant illness susceptibility.

Table 3
Structural equation model showing weighted least squares (WLSMV) estimates of the direct and indirect effect of prenatal vaginal infection on offspring positive psychotic experiences at age 21 (n = 2,329).

Outcome/mediator/prenatal risk	Predictor	USPE	SE	p-Value	SPE
Direct effects					
Psychotic experiences (21 yrs)	Infant illness suscept. (6 months)	0.21	0.06	0.001	0.17
	Gender- female	0.17	0.07	0.023	0.16
Infant illness suscept. (6 months)	Vaginal infection (prenatal)	0.14	0.03	<0.001	0.14
	Smoking (prenatal)	0.20	0.04	<0.001	0.16
	Maternal age (prenatal)	−0.03	0.01	<0.001	−0.20
Vaginal infection (prenatal)	Parity	0.06	0.02	0.001	0.09
	Maternal age (prenatal)	−0.02	0.00	<0.001	−0.11
	Maternal alcohol (prenatal)	0.08	0.03	0.011	0.05
Smoking (prenatal)	Parity	0.05	0.01	0.001	0.09
	Maternal age (prenatal)	−0.02	0.00	<0.001	−0.15
	Maternal education (prenatal)	0.17	0.02	<0.001	0.16
	Maternal alcohol (prenatal)	0.17	0.02	<0.001	0.17
Indirect effects					
Psychotic experiences (21 yrs)	Vaginal infection (prenatal) *Via infant illness suscept.(6 months)*	0.03	0.01	0.004	0.02

Note: The direct effect of prenatal vaginal infection on psychotic experiences was not significant (not shown in table). All estimates are probit regression parameters presented as unstandardised parameter estimates (USPE), standard errors (SE) and p-values, and standardised parameter estimates (SPE).
The bias corrected bootstrapping 95% confidence limits support the unstandardised indirect parameter estimates in the table [USPE = 0.02 (0.01, 0.06)].
Fit indices: CFI = 0.99; TLI = 0.98; RMSEA = 0.010; chi-square = 313.96; D.F = 250; p-value <0.004 (in addition all factor loadings in the model were < 0.05).

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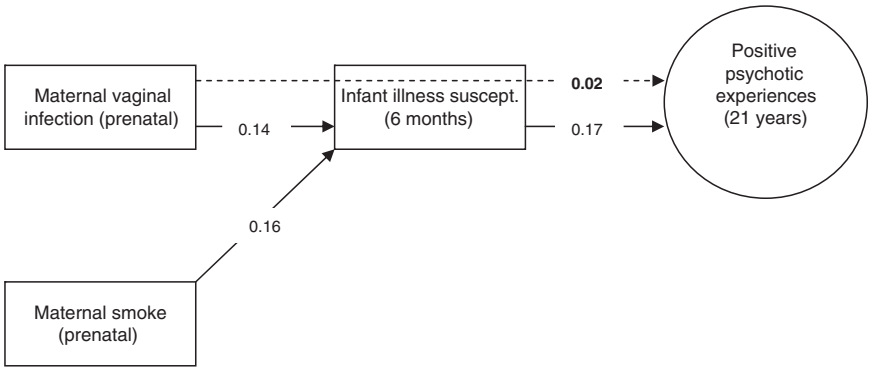

Fig. 2. Structural equation model (i.e., path analysis with latent variables) showing the effects of prenatal maternal vaginal infection and smoking, and infant infections on positive psychotic experiences in offspring at 21 years ($n = 2{,}329$). The direct effect of prenatal vaginal infection on psychotic experiences was not significant (not shown in figure). Showing standardised parameter estimates (all estimates are significant – see Table 3 for p-values). The outcome is the general factor from the bifactor model. The dashed line represents the indirect estimates of vaginal infection > infant illness susceptibility > psychotic experiences. Indirect estimates bolded. Confounding variables not included.

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Contributors

Kim Betts has been designated principal author and was responsible for the bulk of the literature review, drafting, statistical analysis and discussion. Gail Williams assisted with the design of the analysis, provided statistical consultancy and provided support in the interpretation of statistical findings. Jacob Najman is the principal investigator of the MUSP cohort and helped with revision of the manuscript. Rosa Alati and James Scott contributed substantially to the drafting and revision of the manuscript and assisted in the literature review and methodology. All authors had complete access to all data.

Conflict of interest

All authors declare no conflicts of interest exist.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2014.04.013.

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Chapter 7 - Gender-specific response to traumatic events

Exploring the Female Specific Risk to Partial and Full PTSD Following Physical Assault

Published manuscript and formal citation

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Study purpose: This study was designed to physical assault could explain part of the increased risk of clinical and subclinical PTSD in women compared with men.

Supplementary material: Some information relevant to this study (i.e., attrition, IPW and MMI analyses) was published online in a supplementary section only and can be accessed at: http://onlinelibrary.wiley.com/doi/10.1002/jts.21776/suppinfo

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Exploring the Female Specific Risk to Partial and Full PTSD Following Physical Assault

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Previous studies have shown that females are at an increased risk of developing posttraumatic stress disorder (PTSD) in response to physical assault compared with males. Our aims were to (a) test if this gender-specific risk generalised to subclinical levels of PTSD, (b) observe how this relationship was affected by including possible confounding factors, and (c) estimate how this trauma contributed to the overall prevalence of PTSD in females. Data came from an Australian birth cohort study ($n = 2{,}547$) based in Brisbane, Australia that commenced in 1981. Using ordinal logistic regression adjusted for a wide range of confounding factors, including polyvictimisation and internalising and externalising symptoms, we found females were at a significantly greater risk compared to males of developing either partial or full PTSD, odds ratio (OR) = 7.68; 95% confidence interval (CI) = [2.94, 20.08], as well as full PTSD only, $OR = 9.23$; 95% CI = [2.77, 30.79], following the experience of assaultive violence (p value for test of interaction = .004). In addition to the high prevalence of sexual assault (12.9%), attributable risk analysis suggested that due to the strong risk of PTSD in females exposed to physical assault, physical assault is possibly a contributor to the overall female increased prevalence of PTSD.

A growing body of research is showing that trauma events affect males and females differently, with females found to be in general at an increased risk of posttraumatic stress disorder (PTSD) after controlling for trauma type (Breslau, Davis, Andreski, Peterson, & Schultz, 1997; Brewin, Andrews, & Valentine, 2000; Tolin & Foa, 2006) and at a specific and strong increased risk following assaultive violence (Breslau, Chilcoat, Kessler, Peterson, & Lucia, 1999; Jeon et al., 2007). Evidence points to a number of risk factors that may place females at a greater risk of PTSD including gender-specific psychobiological responses to trauma, the younger age at which females experience trauma, negative cognitive appraisal, and lower levels of social support (Olff, Langeland, Draijer, & Gersons, 2007). The increased levels of psychopathology found in women have been suggested as another possible explanation (Breslau et al., 1997; Hapke, Schumann, Rumpf, John, & Meyer, 2006). Psychiatric disorders present prior to the experience of trauma are associated with PTSD vulnerability and increased symptom chronicity (Breslau, 2002; Ehlers, Mayou, & Bryant, 1998; Storr, Ialongo, Anthony, & Breslau, 2007). Another possibility is that greater exposure to a number of different types of traumas, known as polyvictimisation, may be partly responsible for the gender differences in the association. Polyvictimisation is found to be associated with both gender and an increased risk of trauma symptoms (Finkelhor, Orrarod, & Turner, 2007). It is as yet unknown if these risk factors, however, account for part of the gender difference specific to physical assault.

In exploring the causes of gender differences to physical assault further, it may prove useful to examine if this relationship generalises to both full and partial PTSD. By doing so we may gain a fuller picture of how particular traumas affect males and females differently. There currently exists no single accepted definition of partial PTSD (Blanchard, Hickling, Taylor, Loos, & Gerardi, 1994; Marshall et al., 2001; Schnurr, Friedman, & Rosenberg, 1993; Stein, Walker, Hazen, & Forde, 1997). Stein and colleagues (Stein et al., 1997) proposed a restrictive definition of partial PTSD that requires persons to meet the criteria for full PTSD, but needing only one symptom from each of the three clusters of reexperience, hyperarousal, and avoidance/numbing. Using a similar definition, a previous study found females at a far higher risk of both partial and full PTSD than men after experiencing physical assault (Jeon et al., 2007), indicating that

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even at subclinical levels this trauma has a greater impact on females. Importantly, no studies investigating the development of both partial and full PTSD resulting from trauma type have compared these groups against those reporting trauma with no PTSD, in multivariable analysis while also producing separate gender estimates (Copeland, Keeler, Angold, & Costello, 2007; Jeon et al., 2007). By failing to include the third more numerous group "reporting trauma with no PTSD," a clear understanding of the impact of a particular trauma upon the general population is not possible. This is because risks are estimated in isolation of the "reporting trauma with no PTSD" group and important differences between those with partial PTSD and those with no PTSD may go unnoticed.

In this study we tested if the increased risk to PTSD following physical assault in females compared with males is found at subclinical levels of PTSD and described the resulting patterns among the full sample of trauma-exposed participants. We also adjust for a number of factors that may account for the gender-specific risk including prior internalising and externalising symptoms, polyvictimisation, multiple traumatic exposures, age at worst trauma, and socioeconomic indicators. In addition, we estimate the associations separately in males and females depending on the traumas, to determine if physical assault strongly contributes to the overall female increased prevalence of PTSD.

Method

Participants and Procedure

The Mater University Study of Pregnancy (MUSP) is a longitudinal birth cohort, with the original sample consisting of all pregnant mothers attending public obstetric consultations at Brisbane's Mater Misericordiae Hospital (MMH) from 1981 to 1984 ($n = 7{,}223$). The MMH is a large hospital accounting for approximately 50% of births in Brisbane during the catchment period. Although the exclusion of private patients led to a sample skewed towards participants of lower socioeconomic status than the Brisbane average, there were no important differences regarding neonatal outcomes. Further information regarding the MUSP can be found elsewhere (Najman et al., 2005). Subsequent to the initial assessment, a wide range of measurements were collected of mother and child at birth, 6 months and 5, 14, and 21 years after birth, including anthropometric, psychiatric, general health, and socioeconomic indicators. Of the original 7,223 who completed the baseline measurements during pregnancy, 2,547 (35%) of the offspring completed the Composite International Diagnostic Interview (CIDI-Auto; World Health Organisation, 1997a, 1997b) at the 21-year follow-up (49% male and 51% female).

Measures

At the 21-year follow-up, lifetime diagnoses of *DSM-IV* PTSD were ascertained using the lifetime CIDI-Auto version 2.1. The CIDI Auto is a computerised instrument administered by trained interviewers and is considered to have strong validity and reliability (Peters, Clark, & Carroll, 1998). Subjects were asked to nominate the traumatic events they had experienced from a selection of 10 predefined events including exposure to combat or war, a life-threatening accident, a natural disaster, witness to death or injury, rape, sexual molestation, physical assault, threat with a weapon or kidnap, torture or terrorism, other, and disclosure of a friend's trauma (see online supplemental materials for full wording of traumatic events). If multiple events were nominated, the subject was asked to specify the most stressful or upsetting, but if only one event was nominated, the subject was asked if this had happened once or more than once to aid in the recall of which experience had been the worst trauma. Regarding the specified trauma, subjects must have reported that the trauma made them feel terrified or helpless to continue on to be asked a total of 17 questions relating to the experience of three symptom clusters of which participants needed a certain number of symptoms from each to be diagnosed with PTSD. The clusters and number of symptoms required included reexperiencing ≥ 1 of 5, hyperarousal ≥ 2 of 5, and avoidance/numbing ≥ 3 of 7 at a duration of ≥ 1 month and which caused the subject clinically meaningful functional impairment to attain a diagnosis of lifetime PTSD. We used the restrictive definition of partial PTSD according to Stein and colleagues (1997) by which participants must satisfy the same criteria as those with full PTSD (including functional impairment), but need only report one symptom from the three symptom clusters of reexperiencing, hyperarousal, and avoidance/numbing.

We created a composite predictor variable collapsing the 11 trauma categories into five categories; sexual assault, physical assault, noninterpersonal trauma, indirect trauma, and other, which could not include bereavement, illness, business loss, or family conflict. Experiencing combat and being the victim of torture or terrorism were not included as none of the subjects nominated these as their worst trauma. Polyvictimisation was constructed by counting the number of different types of traumas (from the original 11 traumas) a participant had experienced (1, 2, 3, ≥ 4). Multiple exposures to either the same type or different types of trauma (1, ≥ 2), and age at trauma exposure were also collected. Prior internalising and externalising symptoms were ascertained using a shortened version of the child behaviour checklist (CBCL; Achenbach, 1991), explained in detail elsewhere (Bor et al., 1997). Each scale consisted of 10 items completed by mothers at the 5-year follow-up for which answers were chosen from *always/sometimes/never* (e.g., "How often is your child too fearful or anxious?" and "Does your child demand a lot of attention?"). A positive value of internalising ($\alpha = .763$) or externalising ($\alpha = .830$) was selected using cutoffs consistent with the percentage of cases identified in a community sample by Achenbach (approximately 10% for each syndrome; Achenbach, 1991; Bor et al., 1997). At 21 years, socioeconomic indicators of offspring were collected including education level (incomplete secondary school, complete secondary school, attending/complete technical college, attending/complete university), income level

(high, middle, low), and employment type (nonmanual, manual, student, never worked/unemployed).

Data Analysis

Initially, χ^2 tests were used to compare subjects who had been exposed to at least one traumatic event to those with negative exposure status by key descriptive variables including gender, employment, income, alcohol use, and age. After excluding those who had not experienced a trauma, the proportion of participants who developed partial or full PTSD depending on the trauma category were estimated separately for males and females. Next, among those exposed to trauma we examined how the predictors, polyvictimisation, multiple traumatic exposures, age at trauma, and internalising and externalising symptoms were related to gender, including χ^2 tests. Before moving to the regression analysis we restricted the sample to those who had values on all variables of interest, including covariables ($n = 1{,}124$).

When the outcome is ordered, ordinal regression is generally considered more appropriate as the precision of the relationships is improved by accounting for the ordinal nature of the outcome (Ananth & Kleinbaum, 1997). Thus, we used a partial proportional odds model to predict the odds of a subject being diagnosed at two levels of the ordinal outcome variable, with operational definitions as follows: (a) at least partial PTSD (partial or full PTSD vs. no PTSD), and (b) only full PTSD (full PTSD vs. partial or no PTSD). This method was chosen as it allows us to formally test if physical assault is predictive of both partial and full PTSD in females among the entire sample of individuals exposed to trauma. Practically, the use of such a method permitted us to statistically test a second-order interaction allowing the effect on the ordinal levels of the PTSD outcome to vary by the predictors: trauma type and gender. This allowed us to compare how the traumas differently predicted partial and full PTSD separately by gender (additional details of the partial proportional odds procedure carried out using SAS software is available from the corresponding author upon request and can also be found in (Stokes, Davis, & Koch, 2000).

Next we undertook multivariate analyses aimed at determining how this association responds to adjustment by risk factors, which may explain the relationship, including multiple traumas, polyvictimisation, age at worst trauma event, internalising and externalising symptoms at 5 years, and child income, education, and employment at 21 years. We then carried out a multivariate attrition analysis by comparing those with information at 5 years, but who did not attend the CIDI interview at 21 years with those who completed the CIDI by a number of indicators associated with trauma exposure. Finally, among those exposed to trauma and with values on all variables of interest, we performed an attributable risk (AR) analysis to see how the trauma types accounted for the prevalence of PTSD, separately by gender (see online supplemental materials).

Results

One thousand three-hundred eighteen subjects had experienced trauma; the overall sample prevalence of traumatic events was 51.75% (56.9% of males and 46.9% of females) with the overall sample prevalence of full PTSD at 6.32% (3.46% of males and 9.34% of females). Table 1 reveals that risk of trauma experience was higher in those employed in manual jobs, and increased as maternal alcohol consumption increased and income decreased. Males were more likely to be exposed to trauma than females and the risk of trauma experience increased with age. Table 2 shows that the types of trauma experienced varied by gender, with females more likely to report experiencing a sexual assault compared with males, while males were more likely to experience physical assault. Despite the overall rate of trauma being higher among males, females were at a greater risk of developing both partial and full PTSD. The prevalence of full PTSD in subjects reporting trauma was 12.2% (6.1% male and 19.3% female), and the prevalence of subjects reporting partial PTSD was 5.1% (3.3% male and 7.9% female). A

Table 1
Differences in Child Characteristics at 21 Years by Traumatic Event Exposure

	Unexposed		Exposed		
Variable	*n*	%	*n*	%	χ^2
Gender[a]					24.84***
Male	536	43.19	705	56.81	
Female	695	53.06	613	46.94	
Age[b]					11.61*
18–19	402	53.25	353	46.75	
20	553	46.94	625	53.06	
21	247	44.74	305	55.25	
22–23	27	42.55	35	56.45	
Income ($/week)[c]					30.58***
0–299	191	39.79	289	60.21	
300–499	412	46.03	483	53.97	
>499	610	54.03	519	45.97	
Employment[d]					40.6***
Nonmanual	530	49.81	534	50.19	
Manual	348	40.74	506	59.25	
Student	277	58.56	196	41.44	
N.W./other	51	50.50	50	49.50	
Alcohol consumption[e]					25.71***
None	83	53.21	73	46.79	
Light	514	53.32	450	46.68	
Moderate	221	49.11	229	50.89	
Heavy	284	43.16	374	56.84	
Very heavy	116	40.28	172	59.72	

Note. N.W. = Never worked.
[a]$n = 2{,}549$. [b]$n = 2{,}547$. [c]$n = 2{,}504$. [d]$n = 2{,}492$. [e]$n = 2{,}516$.
*$p < .05$. ***$p < .001$.

Table 2
Frequency of Worst Recorded Trauma, Partial, and Full PTSD by Trauma Separately by Gender

	Exposure rate of trauma among total sample (n = 2,547)				Proportion who developed Partial PTSD (n = 1,318)				Proportion who developed Full PTSD (n = 1,318)			
	Males		Females		Males		Females		Males		Females	
Traumatic event	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Sexual	25	2.0	169	12.9	0	0.0	19	11.2	11	44.0	77	45.6
Assaultive	212	17.1	58	4.4	7	3.3	6	10.3	6	2.8	13	22.4
Noninterpersonal	346	27.9	199	15.2	9	2.6	6	3.0	15	4.3	10	5.0
Other	37	3.0	74	5.7	2	5.4	5	6.8	8	21.6	12	16.2
Indirect	85	6.9	113	8.7	5	5.9	8	7.1	3	3.5	6	5.3
Total	705	56.9	613	46.9	23	3.3	44	7.2	43	6.1	118	19.3

Note. PTSD = posttraumatic stress disorder.

far higher proportion of females developed both partial and full PTSD after experiencing physical assault compared to males. Table 3 shows the distribution of the possible risk factors, which may account for the increased risk of PTSD in females by gender, including chi-square tests among participants exposed to trauma. Males had significantly higher levels of polyvictimisation, females were significantly younger at the time of the trauma, and neither gender was more likely to be exposed to multiple traumas. Of the 1,318 subjects reporting trauma, 1,170 and 1,172 had measures of internalising and externalising symptoms at age 5 years respectively, but no significant gender differences were found.

Table 3
Univariate Analyses Showing Distribution of Possible Risk Factors Separately for Males and Females

	Males		Females		
Risk factor	*n*	%	*n*	%	χ^2
Polyvictim[a]					15.07*
1	325	50.62	317	49.38	
2	165	49.85	166	50.15	
3	120	63.83	68	36.17	
≥4	95	60.51	62	39.49	
Age at trauma[a]					46.58***
1–9	47	31.54	102	68.46	
10–14	88	45.13	107	54.87	
15–18	349	56.66	267	43.34	
19–21	221	61.73	137	38.27	
Multiple trauma[a]					2.34
1	254	50.80	246	49.20	
≥2	451	55.13	367	44.87	
Internalising[b]					0.16
Yes	570	54.39	478	45.61	
No	64	52.46	58	47.54	
Externalising[c]					1.09
Yes	558	53.86	478	46.14	
No	78	57.27	58	45.73	

Note. Restricted to participants exposed to trauma at 21.
[a]n = 1,318. [b]n = 1,170. [c]n = 1,172.
*$p < .05$. ***$p < .001$.

Table 4 shows the increased odds of both levels of PTSD associated with the different traumas in females compared with males. Importantly, results from the second-order interaction indicated that the observed pattern by which the odds of the two levels of the PTSD outcome varied differentially by trauma type and gender was significant (p = .002). This significant interaction is mainly due to physical assault, by which females are at a far greater risk of both partial and full PTSD than males. Further, the increased risk of partial PTSD in women compared with men resulting from physical assault, odds ratio (OR) = 8.55, 95% CI = [3.56, 20.52], was not as large as the increased risk of full PTSD in women compared with men resulting from physical assault, OR = 10.46, 95% CI = [3.43, 31.91]. This indicates that the disproportionately increased risk of developing PTSD symptoms in women compared with men due to physical assault is greater at higher levels of symptoms expression. Adjustment for the confounders (Table 5) slightly attenuated the estimates of increased risk in females due to physical assault, but the risk remained stronger at the higher level of symptom expression and the second-order interaction remained significant (χ^2 = 22.73, df = 8, p = .004). The only covariables that significantly predicted the outcome were multiple traumas and polyvictimisation; however, neither had a substantive impact on the association between physical assault and PTSD in females. Importantly, among the sample with values on all variables of interest (n = 2,140), and thus used in the regression analyses, 12.5% had PTSD (6.5% male and 19.4% female) and 4.9% had partial PTSD (2.7% male and 7.5% female).

Table 4
Ordinal Logistic Regressions by Trauma Type for PTSD as a Function of Gender

	Partial and full PTSD			Full PTSD only		
Trauma type	*OR*	95% CI	χ^2	*OR*	95% CI	χ^2
Sexual	1.56	[0.60, 4.06]	0.81	0.91	[0.35, 2.38]	0.03
Assaultive	8.55	[3.56, 20.52]	23.07***	10.46	[3.43, 31.91]	17.04***
Noninterpersonal	1.15	[0.56, 2.38]	0.15	1.36	[0.48, 2.68]	0.08
Other	0.71	[0.28, 1.81]	0.50	0.62	[0.23, 1.74]	0.81
Indirect	1.41	[0.49, 4.07]	0.40	1.10	[0.24, 5.05]	0.01

Note. Restricted to participants exposed to trauma at 21 ($n = 1{,}124$). Wald test for second order interaction: $\chi^2 = 25.16$, degrees of freedom = 8 ($p = .001$). PTSD = posttraumatic stress disorder.
*$p < .05$. ***$p < .001$.

The multivariate attrition analysis revealed that at the 5-year follow-up those included in the study were more likely to have the same male parent as they did at birth and more likely to have mothers who consumed light and moderate to heavy amounts of alcohol compared with children who were lost to follow-up. *P* values for coefficients and for likelihood ratio tests reveal that the two groups did not differ significantly on any of the other indicators (see online supplemental materials). Finally, AR analyses show that had females been exposed to noninterpersonal trauma instead of sexual or physical assault this would have led to a reduction in full PTSD of 87% and 49%, respectively, among females. In contrast, had males been exposed to non-interpersonal trauma instead of sexual or physical assault this would have led to a reduction in full PTSD of 56% and −23%, respectively, among males (see online supplemental materials).

Discussion

Our findings show that women were at a much greater risk of partial and full PTSD after experiencing physical assault when compared with males, and that this gender-specific risk is greater at higher levels of PTSD. We also found no gender-specific risks resulting from the other traumas. Our results suggest that the increased risk of PTSD in females found to result of preexisting psychopathologies prior to trauma exposure (Breslau et al., 1997; Hapke et al., 2006), may not play a role specific to the gender-specific risk of PTSD resulting from physical assault. For the first time, we tested whether polyvictimisation changed the strength of the gender-specific effect, and found that it did not. Also, the increased prevalence of sexual assault among females has long been known to account for part of the increased female prevalence of PTSD (Tolin & Foa, 2006). Attributable risk analysis, however, indicated that despite the low prevalence of physical assault in females compared with males, the greatly increased risk of PTSD in female assault victims compared with male assault victims resulted in physical assault contributing to a far greater proportion of the PTSD prevalence in females than the PTSD prevalence in males. Hence, physical assault is possibly a contributor to the increased prevalence of PTSD in females compared with males, though these results must be viewed in the light of the limitations of our AR analysis. Together, these findings provide new insights into the observed increased risk of PTSD found in women following assaultive violence (Breslau & Anthony, 2007; Breslau et al., 1999, 1997; Frans, Rimmo, Aberg,

Table 5
Ordinal Logistic Regressions by Trauma Type for PTSD as a Function of Gender With Control Variables in the Models

	Partial and full PTSD			Full PTSD only		
Trauma Type	*OR*	95% CI	χ^2	*OR*	95% CI	χ^2
Sexual	0.94	[0.33, 2.69]	0.01	0.53	[0.19, 1.52)	1.39
Assaultive	7.68	[2.94, 20.08]	17.28***	9.23	[2.77, 30.79]	13.09*
Noninterpersonal	0.96	[0.45, 2.06]	0.01	0.94	[0.39, 2.27]	0.02
Other	0.94	[0.32, 2.75]	0.01	0.80	(0.27, 2.34]	0.17
Indirect	1.69	[0.53, 5.31]	0.79	1.34	[0.27, 6.55]	0.13

Note. $n = 1{,}124$. PTSD = posttraumatic stress disorder. Control variables include multiple traumas, polyvictimisation, age at worst trauma event, internalising and externalising symptoms at 5 years, and child income, education and employment at 21 years. Wald test for second order interaction: $\chi^2 = 22.73$, $df = 8$ ($p = .004$)
*$p < .05$. ***$p < .001$.

& Fredrikson, 2005; Hapke et al., 2006). This finding is of concern because our sample is young, meaning that much physical assault is yet to be perpetrated, particularly that resulting from intimate partner violence.

The mechanisms by which female gender increases the risk of developing partial and full PTSD due to physical assault are still unknown. One possible explanation comes from studies which found that elevated perceived distress and elevated avoidance/numbing symptoms explained the overall increased risk and specific increased risk due to physical assault of PTSD respectively (Breslau et al., 1999; Frans et al., 2005). Our results add to this evidence, as we found that at higher levels of symptoms expression the increased female risk to physical assault compared with males is more pronounced than at lower levels of symptoms expression. This may suggest that gender-specific psychological processes leading to higher levels of distress and avoidance/numbing in females, may partly cause the increased risk of PTSD (Breslau et al., 1999; Frans et al., 2005). These results also suggest that these same psychological processes operate at lower levels of PTSD symptom expression, as even at subclinical levels females remained at far greater risk. Alternatively, it is possible that both the increased risk of PTSD and increased distress and avoidance/numbing among females who experienced physical assault may result from the more severe nature of female–victim physical assaults. Compared with male-victim assaults, female-victim assaults are more likely to be perpetrated by an intimate partner, result in serious injury, and involve the threat of sexual violence (Pratchett, Pelcovitz, & Yehuda, 2010; Tolin & Foa, 2006). Unfortunately our version of the CIDI did not collect information regarding the type of physical assault experienced. Future studies with such capacity should compare differences in both the type of physical assault experienced and subsequent psychological responses expressed by women who develop no, partial, and full PTSD.

There is increasing evidence that the current definition of *DSM-IV* PTSD is overly restrictive (Mylle & Maes, 2004), particularly in relation to diagnosing the symptoms of traumas which occurred in younger people (Copeland et al., 2007). In this study we employed the definition of partial PTSD originally proposed by Stein and colleagues (Stein et al., 1997), which requires the involvement of all three symptom clusters, unlike other definitions that require various combinations of only two of the three symptom clusters to be present (Blanchard et al., 1994; Schnurr et al., 1993) or less traditional approaches (Marshall et al., 2001). The definition of partial PTSD we used is likely to have resulted in the identification of far fewer subjects with partial PTSD, with this smaller group likely to have more serious trauma related symptoms and impairment (Mylle & Maes, 2004). As pointed out in this same study (Mylle & Maes, 2004) we also found it was often unclear whether previous studies using a definition similar to ours (Breslau, Lucia, & Davis, 2004; Jeon et al., 2007) or an alternative definition (Blanchard et al., 1994; Marshall et al., 2001; Schnurr et al., 1993) required minimum symptom duration of $\geq$1 month (Criterion E) and/or functional impairment (Criterion F) for partial diagnosis. Given the uncertainties surrounding the definition and clinical utility of partial PTSD, we adhered to these restrictions, employing a conservative definition and found it endemic only among female assault victims. This may point to an important, but as yet unknown relationship between physical violence and serious levels of female subclinical PTSD, perhaps requiring acuminous clinical attention even in the absence of a full diagnosis.

Our study was not without limitations. First, we relied on retrospective reports of trauma exposure and PTSD symptoms. Based on recent findings (Moffitt et al., 2010) we expect that the prevalence of lifetime full and partial PTSD would have been greater had we the capacity to assess PTSD prospectively throughout childhood and adolescence. Such underreporting may lead to recall bias in etiological studies which rely on lifetime prevalence (Moffitt et al., 2010). Despite the relatively high prevalence of both trauma exposure and PTSD among our participants it is possible that those who experienced PTSD symptoms early in life and for shorter duration underreported PTSD symptoms. Therefore, our findings await corroborating evidence from studies with the capacity to test our hypothesis using repeated measures of PTSD. Second, we had measures of child behaviour problems at 5 years of age, but did not have prior psychiatric disorders diagnoses, which may explain why our results differed to studies that used such diagnoses (Breslau et al., 1997; Hapke et al., 2006).

Third, the MUSP has been subject to attrition, retaining 35% of the original sample for psychiatric interviews at 21, resulting from the failure to contact many participants. Overall, attrition in the MUSP has been associated with lower socioeconomic status, potentially underestimating associations by disproportionately losing those with worse health, a scenario of particular concern when the predictor is subject to attrition (Najman et al., 2005). When we compared the large number of subjects who had been lost to follow-up with those not lost, however, the two groups did not differ significantly on many key indicators that are likely to be linked to an increased risk of trauma exposure (the predictor). Those not lost were more likely to have the same father at 5 years than they had at birth, possibly a protective factor, and more likely to have mothers who consumed moderate and larger quantities of alcohol, possibly a risk factor. Although we were therefore unable to find strong evidence that our results would be affected by attrition bias, caution must be exercised when interpreting our results. Finally, our aims presented challenges that must be considered when interpreting the results of our AR analysis. Although most diseases have a background prevalence amongst unexposed participants, this is not the case with PTSD, which requires an individual to be exposed to qualify for the disorder. Thus, because it is not possible to compute a multivariate OR when the reference (unexposed) category has no cases, we could not compare the proportion of the outcome avoided if individuals exposed to a particular trauma had not been exposed to trauma at all. Instead, we chose to use noninterpersonal trauma as the reference as it offers a substantive comparison against the two interpersonal traumas

of physical and sexual assault. We also chose this trauma because it comprises a stricter definition than other and indirect traumas, both of which include nonspecified traumas experienced by the participant or by the participants' family member or friend, respectively. Related to this is the limitation that the male and female ARs are not directly comparable, as they are based on reference traumas with different risks and prevalences dependent on gender. With these limitations in mind, however, the results still show that compared to traumas where interpersonal violence does not feature, physical assault in females accounted for a large portion of the outcome, while in males the relationship was reversed, suggesting even at a low prevalence physical assault could be part of the reason for the overall female increased risk of PTSD.

We determined in a prospective population-based sample of young adults exposed to trauma that the relationship between physical assault and the increased risk of PTSD in females compared with males is found at subclinical levels of PTSD, and that this gender-specific risk is greater at higher levels of PTSD. We also found that despite the relatively low prevalence of physical assault among females, this trauma possibly makes a contribution to the overall female increased prevalence of PTSD. Therefore, in addition to efforts made to reduce physical violence perpetrated against women, efforts should be made to discover the mechanisms, whether involving a greater specification of the assault or the gender-specific psychological response, so to better target preventative efforts and inform therapeutic intervention. Such efforts may be enhanced by employing subclinical PTSD to help establish dose-response relationships between risk factors with the level of PTSD.

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Pre-trauma verbal ability at five years of age and the risk of post-traumatic stress disorder in adult males and females

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Study purpose: This paper investigated a second factor which may help account for the increased risk of PTSD in females compared with males, that being childhood cognitive ability.

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Pre-trauma verbal ability at five years of age and the risk of post-traumatic stress disorder in adult males and females

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ABSTRACT

Previous studies have shown that high cognitive ability, measured in childhood and prior to the experience of traumatic events, is protective of PTSD development. Our aim was to test if the association between pre-trauma verbal ability ascertained at 5 years with DSM-IV lifetime post-traumatic stress disorder (PTSD) at 21 years was subject to effect modification by gender, trauma type or prior behaviour problems. Using a prospective birth cohort of young Australians, we found that both trauma type and behaviour problems did not change the association between cognitive ability and PTSD. During multivariate analysis, testing for the interactive effect of gender revealed that verbal ability was linearly and inversely associated with PTSD in females only, with those in the lowest verbal ability quintile having strongly increased odds of PTSD (OR = 3.89: 95% CI; 1.50, 10.10) compared with those in the highest quintile. A graph of the interaction revealed lower verbal ability placed females, but not males, at an increased risk of PTSD. Our results indicate that lower verbal ability in early childhood is a vulnerability factor for PTSD in females but not in males, and may constitute a gender-specific risk factor responsible for part of the increased risk of PTSD found in females compared with males.

1. Background

Epidemiological research has found an inverse relationship between cognitive ability with morbidity and mortality. Individuals with a lower cognitive ability have an increased risk of a number of conditions in later life including schizophrenia (Zammit et al., 2004), depression, hypertension, lung disease (Der et al., 2009), increased depression persistence and comorbidity (Koenen et al., 2009). However, the mechanisms by which cognitive ability may lead to a decline in individual health outcomes over time remains unclear and intercorrelated with a number of environmental and developmental factors. For this reason, even studies which have conducted extensive cognitive testing prior to the onset of poor health (pre-morbid testing) and controlled for important related affects including socio-economic position (SEP), familial circumstances and indicators of fetal and child development are unable to completely rule out possible residual confounding due to these factors (Batty et al., 2007; Batty et al., 2009; Der et al., 2009).

Despite this, different health outcomes are arguably more or less directly linked to pre-morbid measures of cognitive ability. In this regard, findings from a number of prospective and well-controlled studies of military populations, which suggest a causal link between pre-trauma cognitive ability and Post-Traumatic Stress Disorder (PTSD), appear relatively robust to confounding owing in part to the clearly defined principle determinant of the disorder (combat exposure). This evidence suggests that various measures of pre-combat cognitive ability predict PTSD risk in returned soldiers (Kremen et al., 2007; Macklin et al., 1998; Gilbertson et al., 2006; Marx et al., 2009)

Regarding the mechanism by which lower cognitive ability may result in a greater risk of PTSD, these papers offer multiple explanations owing partly to the variety of neurocognitive performance measures used to predict PTSD. Three studies suggest that higher cognitive ability (Kremen et al., 2007; Macklin et al., 1998) and a high capacity to effectively and flexibly manipulate verbal information (Gilbertson et al., 2006) reduce the negative impact of trauma on the individual by increasing their ability to process and build meaning from their trauma. Another paper suggests that high visual-spatial memory affords the individual an increased capacity in the initial

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acquisition of the visual aspects of the traumatic episode, which aides in rehearsal and later habituation to the trauma (Marx et al., 2009).

While military studies have the advantage of being well-controlled and often use sophisticated testing, participants are typically recruited at the age of enlistment. Although this does not affect the ability of these studies to demonstrate an association between cognitive ability and PTSD, environmental factors and circumstances during childhood and adolescence are unavailable or collected retrospectively. This may result in misspecification during analysis and decreased ability to interpret temporal relationships between cognitive ability and PTSD.

To date, there have been only three prospective, population-based studies that have been able to investigate these life course factors. One study from Storr et al. has found no association between early scholastic ability and PTSD (Storr et al., 2007). The other two studies have found inverse associations between cognitive ability with PTSD risk in late adolescence (Breslau et al., 2006) and early adulthood (Koenen et al., 2007). There were some methodological weaknesses in the studies where associations were found. The first study assessed PTSD when the participants were 17 years of age and yet to pass through the peak period of trauma exposure, affecting generalisability to young adults and also resulting in the identification of very few PTSD cases (Breslau et al., 2006). The second study did not account for trauma type (Koenen et al., 2007). Trauma type is likely to play a confounding role in the relationship between child cognitive ability with PTSD risk, as measures of cognitive and scholastic ability have been found to predict the type of traumas a young person will subsequently experience (Breslau et al., 2006; Storr et al., 2007), and specific types of trauma are highly predictive of PTSD outcomes (Breslau et al., 1999; Brewin et al., 2000; Frans et al., 2005). Additionally, individuals in this study were classed as trauma exposed only if they had experienced an acute reaction to the trauma (criterion A2). This resulted in those who were potentially the most resilient individuals (those who experienced trauma but reported no immediate reaction) being classified as unexposed to trauma (Koenen et al., 2007). A final limitation relevant to both studies was the use of sample sizes too small to permit testing for gender differences. Emerging evidence is showing that gender interacts differently in the relationship between cognition and a range of mental health outcomes. One recent study (Glaser et al., 2011) found that the relationship between cognitive ability and depression in men and women changes over time, especially around puberty, and differs for males and females. Another study (Hatch et al., 2007) found that lower cognitive ability was associated with higher internalizing symptoms in women only. Although neither study assessed PTSD as an outcome, these findings show the need to assess whether the relationship between cognitive ability and PTSD is present only in females, as found previously by these studies in relation to other mental health outcomes.

In this study, we use data from a large prospective birth cohort study to test the hypothesis that verbal ability at 5 years of age according to the Peabody Picture Vocabulary Test-Revised (PPVT-R) is inversely associated with the risk of DSM-IV lifetime PTSD at 21 years of age. We will take into account a range of developmental and environmental characteristics and expand the existing evidence, by testing for the role of gender, trauma type and behaviour problems in the association between verbal ability and PTSD.

2. Materials and methods

2.1. Sample and data

Participants were from the Mater University Study of Pregnancy (MUSP), a prospective birth cohort based in Brisbane, Australia. Between 1981 and 1984 a total of 7223 pregnant mothers were recruited from the Mater Misericordiae Hospital. The first wave of data collection occurred before the birth of the child, after which subsequent data collections were carried out on both mother and child at birth and 6 months, 5, 14 and 21 years after birth. Further information regarding the MUSP has been detailed previously (Keeping et al., 1989; Najman et al., 2005). At 21 years of age, 2547 (35%) of the offspring completed the Composite International Diagnostic Interview (CIDI-Auto) (49% male and 51% female). Of these, 1010 (125 PTSD cases) participants reported trauma exposure and had complete data for multivariable analysis. Informed consent was gained from all participants, all data was coded for confidentiality and ethics was approved for the cohort was approved by the institution and funding body.

2.2. Measurement of verbal ability

The Peabody Picture Vocabulary Test-Revised (PPVT-R) was administered to children at the five year follow-up. The test requires the examinee to indicate which one of four pictures best describes a word which the examiner expresses verbally, with the resulting score used as a measure of the subject's verbal intelligence (Jongsma, 1982). The PPVT-R has been validated against other standardised intelligence tests used on children (Childers et al., 1994; Dunn, 1981; Johnson et al., 1993).

2.3. Measurement of PTSD

At the 21 year follow-up, participants were screened for DSM-IV lifetime Post-Traumatic Stress Disorder (PTSD) (First and Tasman, 2004) using the Composite International Diagnostic Interview (CIDI-Auto) Version 2.1 (World Health Organisation, 1997). The CIDI-Auto was administered by trained interviewers and has been found to have good validity and reliability (Peters et al., 1998). Individuals who experienced one or more of the eleven possible traumatic events were asked further questions regarding the presence of 17 PTSD symptoms from three distinct categories including re-experiencing, hyperarousal and avoidance, in addition to questions assessing the level of functional impairment caused by the symptoms. Importantly, participants needed to have reported an acute reaction to trauma (criteria A2) to be diagnosed with PTSD, but not to be classed as trauma exposed. For participants who experienced multiple traumas, PTSD was assessed with regard to the most 'stressful or upsetting' event. No participants designated combat exposure or being victim of torture or terrorism as their most stressful or upsetting event. We created a four category trauma exposure variable consisting of (1) interpersonal victimisation (rape, molestations, physical assault, threatened with a weapon or kidnapped), (2) interpersonal victimisation and at least one more traumatic exposure (3) non-interpersonal victimisation (accident, witness to death/injury, natural disaster, other) and (4) non-interpersonal victimisation and at least one more traumatic exposure.

2.4. Measurement of confounding factors

Birth weight, maternal age at birth and parity were selected *a priori* to be included in all models due to earlier findings from this cohort reporting an inverse association between birth weight and a number of mental health and behaviour problems (Alati et al., 2007; Alati et al., 2009; Betts et al., 2011) and because of its central role in the proposed mechanism (Gale et al., 2009). We constructed birth weight *z*-scores which were internally adjusted for gender and gestational age as a crude measure of fetal development. Birth weight and gestational age (in weeks) were taken

from obstetric records at the time of birth, along with maternal age at birth and parity.

We selected other covariables based on the previous prospective and military studies (Breslau et al., 2006; Gale et al., 2008; Gilbertson et al., 2006; Koenen et al., 2007; Kremen et al., 2007; Macklin et al., 1998; Marx et al., 2009; Storr et al., 2007; Thompson & Gottesman, 2008). Internalising and externalising behaviour problems were assessed in the offspring at 5 years using a shortened version of the child behaviour checklist (CBCL) (Achenbach, 1991a) completed by mothers, fully described elsewhere (Bor et al., 1997). At 14 years internalising and externalising behaviour was assessed using the Youth Self Report (YSR) (Achenbach, 1991b) completed by the children, and shown previously to have good validity and reliability in the MUSP cohort (Alati et al., 2008). We were only interested in behaviour problems which developed before exposure to trauma and thereby did not originate as part of a PTSD sequelae. Individuals exposed to trauma before 5 were excluded from analyses, individuals exposed to trauma between 5 and 14 were designated as having a behaviour problem according to the CBCL (measured at 5 years), individuals exposed to trauma after 14 were designated as having a behaviour problem according to the YSR (measured at 14 years). As done in previous studies, at both 5 and 14 years the highest scoring 10% of the sample were categorised as having either an internalising or externalising behaviour problem (Alati et al., 2008; Bor et al., 1997). Family income and maternal education were measured at baseline. At the time of birth, maternal anxiety and depression symptoms were ascertained using the Delusions-States-Symptoms Inventory (DSSI) (Bedford & Folds, 1977). The DSSI has been found to correlate well with the Edinburgh Postnatal Depression Scale (EPDS) and the Hospital Anxiety/Depression Scale (Bedford & Deary, 1999). As in previous studies, symptoms of anxiety and depression were defined as having four or more symptoms (Alati et al., 2009). At five years maternal use of alcohol and tobacco were used as indicators of maternal life style.

2.5. Statistical analysis

We began by testing if PPVT-R as a continuous variable predicted (1) exposure to trauma among the full sample ($n = 2547$) using univariate logistic regression, and (2) the type of trauma among those exposed to trauma ($n = 1010$) using univariate multinomial regression. We used univariable logistic regression to test the associations between DSM-IV lifetime PTSD with the PPVT-R quintiles and the confounders. We used a backwards elimination method in which all the covariables found to be significantly associated with PTSD from the univariable analysis were entered into a single model. Variables were subsequently removed from the model one-by-one, removing those with the weakest association first. The final model included all variables with significant coefficients at the $p < 0.05$ level as well as all *a priori* confounders, included in all models. The PPVT-R scores were entered into the final model firstly as quintiles using the highest performing quintile as the reference category, and then separately as a continuous variable in which the odds of PTSD was calculated per one quintile increase in the PPVT-R score.

We tested a number of interactions including gender, prior behaviour problems and trauma type in separate, fully adjusted models in which the PPVT-R was entered as a continuous variable. As we found a significant interaction by gender, we then presented gender estimates separately. We used multivariate logistic regression to compare the odds of individuals being included in the study to those lost to follow-up by the variables included in the final model, and replicated the final analysis using inverse probability weighting to adjust for loss to follow-up (see supplementary sections).

3. Results

When we assessed whether PPVT-R predicted firstly trauma exposure, and then trauma type, all results were non-significant (available upon request). In unadjusted analyses, there was evidence of a linear relationship between the PPVT-R quintiles and PTSD, with a significant difference observed in the odds ratio between the highest and lowest quintiles (Table 1). Females were at a significantly increased risk of being diagnosed with PTSD and birth weight was inversely associated with PTSD risk. Those reporting the experience of interpersonal victimisation and had experienced more than one trauma were at a greatly increased risk of PTSD compared with those who reported only a single experience of non-interpersonal victimisation. While prior internalising behaviour and maternal tobacco use at 5 years were significantly associated with the odds of PTSD diagnosis in univariate analyses (Table 2), in multivariate analyses they produced non-significant coefficients ($p > 0.1$) and were excluded.

The relationship between PPVT-R and PTSD remained after adjustment for gender, trauma type and birth weight adjusted for gestational age, maternal age at birth and parity. We found evidence of a gender interaction in the association between PPVT-R and PTSD. The interaction term showed that females were at a differentially increased risk of PTSD due to decreasing PPVT-R compared with males, in both univariate ($p = 0.028$) and fully adjusted analyses ($p = 0.049$). After adjustment, females in the lowest cognitive functioning quintile had strongly increased odds of PTSD (OR = 3.89: 95% CI; 1.50, 10.10) compared with those in the highest functioning quintile (Table 3). There was no evidence of an association in males. Graphing the linear regressions of the predicted values for males and females separately (Fig. 1) revealed that females were at increased risk of PTSD compared with males due to lower cognitive functioning.

We found no evidence that trauma type or prior behaviour internalising or externalising problems modified the relationship between PPVT-R and PTSD. Multivariate attrition analysis showed

Table 1
Univariable associations between lifetime DSM-IV PTSD with PPVT-R quintiles and *a priori* selected confounders [expressed in OR with 95% Confidence Intervals (CI)].

Predictor	Prevalence % (n)	Odds ratio (95% CI)	p Value
Peabody quintiles	($n = 1010$)		
Quintile 1	17.6% ($n = 178$)	2.02 (1.08, 3.79)	0.028
Quintile 2	21.8% ($n = 220$)	1.64 (0.88, 3.06)	0.116
Quintile 3	18.6% ($n = 188$)	1.59 (0.83, 3.02)	0.162
Quintile 4	20.9% ($n = 211$)	1.52 (0.81, 2.87)	0.194
Quintile 5	21.1% ($n = 213$)	1.00	
Gender	($n = 1318$)		
Female	46.5% ($n = 613$)	3.67 (2.54, 5.30)	<0.001
Male	53.5% ($n = 705$)	1.00	
Trauma type	($n = 1318$)		
Int. victim multiple	25.3% ($n = 333$)	13.38 (7.02, 25.49)	<0.001
Int. victim	9.9% ($n = 131$)	2.69 (1.11, 6.49)	0.028
Non-int. victim multiple	36.8% ($n = 485$)	3.17 (1.61, 6.230	0.001
Non-int. victim	28.0% ($n = 369$)	1.00	
Birth weight *z*-score	($n = 1318$)	0.82 (0.68, 0.97)	0.023
Maternal age at birth	($n = 1318$)		
13–19	15.0% ($n = 198$)	1.87 (0.79, 4.43)	0.157
20–34	79.7% ($n = 1050$)	1.16 (0.52, 2.59)	0.715
35+	5.3% ($n = 70$)	1.00	
Previous births	($n = 1318$)		
Three or more	10.6% ($n = 140$)	1.03 (0.58, 1.82)	0.922
One or two	49.0% ($n = 646$)	1.07 (0.75, 1.52)	0.716
None	40.4% ($n = 532$)	1.00	

Table 2
Univariable associations between lifetime DSM-IV PTSD with confounding factors [expressed in OR with 95% confidence intervals (CI)].

Predictor	Prevalence % (*n*)	Odds ratio (95% CI)	*p* Value
Internalising behaviour	(*n* = 1267)		
Yes	16.4% (*n* = 208)	1.55 (1.02, 2.35)	0.041
No	83.6% (*n* = 1059)	1.00	
Externalising behaviour	(*n* = 1267)		
Yes	15.9% (*n* = 202)	1.20 (0.77, 1.88)	0.417
No	84.1% (*n* = 1065)	1.00	
Maternal anxiety	(*n* = 1315)		
Yes	9.7% (*n* = 128)	1.58 (0.96, 2.58)	0.070
No	90.7% (*n* = 1187)	1.00	
Maternal depression	(*n* = 1315)		
Yes	3.2% (*n* = 42)	0.97 (0.38, 2.52)	0.958
No	96.8% (*n* = 1273)	1.00	
Maternal alcohol (/day)	(*n* = 1165)		
None	19.5% (*n* = 227)	1.00	
>0–0.5	63.4% (*n* = 738)	1.28 (0.80, 2.08)	0.307
>0.5–1.00	10.4% (*n* = 121)	1.11 (0.55, 2.23)	0.776
>1.00	6.8% (*n* = 79)	1.09 (0.48, 2.45)	0.840
Maternal tobacco (/day)	(*n* = 1163)		
None	60.3% (*n* = 701)	1.00	
Smoker	20.6% (*n* = 240)	1.81 (1.18, 2.76)	0.006
Heavy smoker	19.1% (*n* = 222)	1.80 (1.17, 2.79)	0.008
Maternal education	(*n* = 1309)		
High school incompleted	17.7% (*n* = 232)	1.29 (0.74, 2.26)	0.375
Completed high school	64.4% (*n* = 843)	1.17 (0.74, 1.87)	0.491
Completed tertiary study	17.9% (*n* = 234)	1.00	
Family income	(*n* = 1241)		
Low	32.5% (*n* = 403)	1.33 (0.75, 2.37)	0.329
Middle	55.5% (*n* = 689)	0.98 (0.56, 1.71)	0.935
High	12.0% (*n* = 149)	1.00	

that those in the lower quintiles of cognitive functioning were differentially lost to follow-up at the 21 year follow-up compared with those in the higher quintiles (Table 4). The results of the inverse probability weighting analysis showed increased odds of developing PTSD in females with the lowest performing quintile compared with females in the highest quintile [OR 4.26; 95% CI 1.88, 9.65] (Supplementary Table 1). All point estimates were similar to those presented in the final model of our complete case analysis.

4. Discussion

This study aimed to determine if higher levels of verbal ability in early childhood, measured by the PPVT-R prior to trauma exposure, protected trauma exposed individuals against the risk of developing PTSD in later life. We found gender differences such that a linear and inverse relationship between childhood verbal ability and PTSD affected females only. These results suggest that lower verbal ability at five years of age increases the risk of young adult females to develop PTSD after experiencing traumatic situations. Our results confirm the findings of two previous studies, which both identified an inverse association between child cognitive ability and PTSD (Koenen et al., 2007), but also add to this new evidence, as our large sample size allowed capacity to test for several interactions. This is the first time that a population study, with enough power to test for a gender interaction has found a gender difference in the association between cognitive abilities and PTSD. One previous study which tested for this interaction, perhaps did not have the sample size capacity to detect a difference (Breslau et al., 2006). The relationship we found was independent of a range of socio-economic and lifestyle measures and indicators of fetal and child development which were collected prospectively. These included indicators of prior psychopathology which unlike an earlier study did not affect the association between cognitive ability and PTSD (Breslau et al., 2006). Further, the inclusion of birth weight adjusted for gestational age slightly weakened the association, but did not confound it, suggesting that cognitive ability in childhood and later PTSD may not be linked via impaired neural development during fetal growth (Gale et al., 2009).

The mechanism by which lower cognitive ability may result in a greater risk to PTSD is still largely unknown and explanations vary depending on the measure of neurocognitive performance used. Military studies, which employ sophisticated measures of neurocognitive performance unsuitable for use in young children, coupled with the use of combat as a clearly defined determinant of PTSD, provide some of the strongest available evidence concerning the mechanism behind the association. Some of these studies suggest that higher cognitive ability may allow the individual to better translate their trauma into a narrative, and in this way make meaning of the experience, allowing the individual to overcome the trauma (Gilbertson et al., 2006; Kremen et al., 2007; Macklin et al., 1998). While we might expect an increased verbal ability to assist an individual in making meaning of their trauma, our finding that cognitive ability predicts PTSD in females only is difficult to interpret, as these military studies have demonstrated strong associations exist in males (Gilbertson et al., 2006; Kremen et al., 2007; Macklin et al., 1998).

In addition to the above inconsistency, civilian studies have found that cognitive ability plays a role in the development of many types of psychopathology (Gale et al., 2008; Glaser et al., 2011; Hatch et al., 2007; Koenen et al., 2009). Therefore, we must consider that the association we found may be part of a broader relationship by which cognitive ability plays a dynamic role in the development of many psychopathologies across the lifespan. Viewed from this perspective, lower cognitive ability may constitute a general vulnerability to mental illness, with specific aspects

Table 3
Multivariate associations between PPVT-R quintiles and lifetime DSM-IV PTSD at age 21 years separately by gender [expressed in OR with 95% confidence intervals (CI)] (complete case analysis *n* = 1010).

PPVT-R	Unadjusted		Fully adjusted[a]	
	Females	Males	Females	Males
Quintile 1	4.20 (1.83, 9.64)	0.78 (0.26, 2.320	3.89 (1.50, 10.10)	0.77 (0.25, 2.40)
Quintile 2	2.23 (0.99, 4.98)	0.90 (0.32, 2.570	2.22 (0.90, 5.45)	0.81 (0.27, 2.40)
Quintile 3	2.06 (0.89, 4.78)	1.03 (0.36, 2.93)	2.43 (0.95, 6.20)	0.94 (0.32, 2.78)
Quintile 4	1.99 (0.87, 4.54)	0.93 (0.32, 2.64)	2.53 (1.01, 6.36)	0.97 (0.33, 2.85)
Quintile 5	1.00	1.00	1.00	1.00
Linear term	0.75 (0.63, 0.90)	1.05 (0.83, 1.34)	0.79 (0.65, 0.97)	1.07 (0.83, 1.37)
P value	0.002	0.677	0.022	0.592
P for linear PPVT-R by gender interaction	0.028		0.049	

[a] Adjusted for trauma type, birth weight z-score, maternal age and parity.

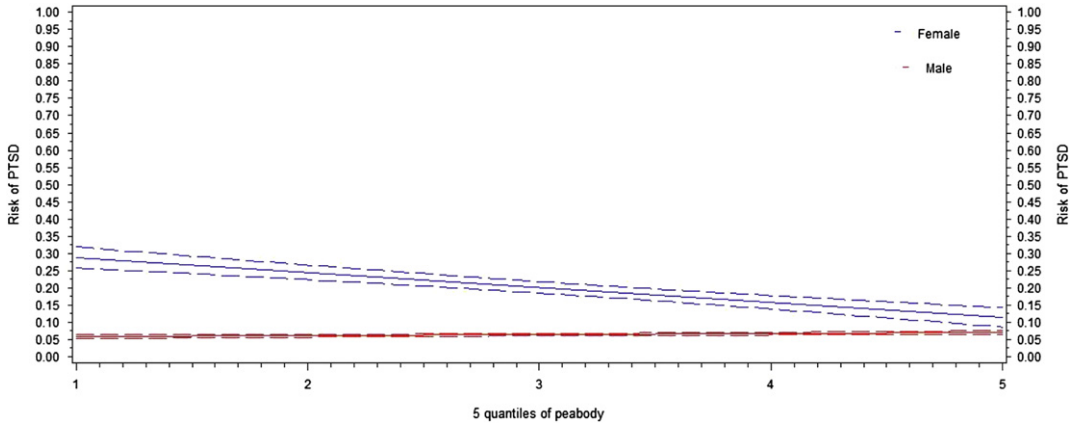

Fig. 1. Multivariate associations between PPVT-R quintiles [highest functioning group (5), to lowest functioning group (1)] at 5 years and lifetime DSM-IV PTSD at age 21 years separately by gender. The predicted values were calculated on 551 males and 459 females (complete case analysis $n = 1010$) and are adjusted for all variables in the final model. Both linear regression lines include 95% confidence intervals (dashed lines).

of cognitive ability having impacts upon specific types of mental illness, perhaps also dependent upon gender and the period of development in which measurements are taken. In further support of this notion, two papers based on two large birth cohort studies found significant gender differences between higher cognitive ability in childhood and decreased mental health symptoms at multiple ages in adolescence and adulthood (Glaser et al., 2011; Hatch et al., 2007). One of these studies found the relationship changed depending on the age and gender of the participants (Glaser et al., 2011). Cognitive ability was positively associated with depression at ages 13 and 14, but this relationship changed in females by age 17 but not in males (Glaser et al., 2011). The other study of adults in their fifties found higher cognitive ability was protective of depression and anxiety in females only (Hatch et al., 2007). Our study is the first to suggest that similar processes may apply to pre-trauma cognitive functioning and the development of PTSD after experiencing a traumatic event. Importantly however, both of these studies interpret their findings as higher cognitive functioning having a protective effect on female mental health symptoms, while males are not benefited by higher cognitive functioning. Our graph on the other hand reveals that males and females have a similar risk of PTSD at higher levels of verbal ability, but that as verbal ability declines the risk of PTSD for females increases linearly, while that of males remains stable. Our study had a number of strengths, the most notable of which was an increased capacity to perform tests of gender interaction. We were also able to account for trauma type with increased specificity compared with previous studies (Breslau et al., 2006; Koenen et al., 2007; Storr et al., 2007) by controlling for multiple trauma exposure, which has been shown to increase the risk of PTSD (Copeland et al., 2007). Another important strength was the age at which we attained measures. Both the PPVT-R and behaviour problems were measured at 5 years. For all but a few who were removed from our analyses, this was prior to the age at which trauma was reported to have occurred. Trauma experience and PTSD symptoms were taken at 21 years, meaning this sample had passed through the point of late adolescents, found to be the peak period of trauma exposure in young people (Breslau et al., 2006).

Table 4
Multivariate attrition analysis comparing those included in the analysis versus those lost since the 5 year follow-up and showing the odds of *not* being included in the study by variables included in the multivariate model [expressed in OR with 95% confidence intervals (CI)] (complete case analysis $n = 3999$).

Effect	OR (95% CI)	*P* value	*P* for LRT
PPVT-R quintiles	*Reference: quintile 5*		
Quintile 1	1.74 (1.43, 2.12)	<0.001	
Quintile 2	1.26 (1.04, 1.53)	0.021	
Quintile 3	1.47 (1.19, 1.80)	<0.001	
Quintile 4	1.04 (0.86, 1.27)	0.676	<0.001
Offspring gender	Reference: male		
Female	0.79 (0.70, 0.90)	<0.001	<0.001
Birth weight *z*-score	Reference: male		
1 SD increase	0.97 (0.91, 1.04)	0.382	0.382
Mother's age at birth	Reference: male		
1 year increase	0.89 (0.77, 1.04)	0.144	0.144

As discussed earlier, of direct relevance to any purported mechanism is the measure of cognitive ability. A limitation of our analysis may be the PPVT-R, which despite being validated against other standard intelligence tests for children and considered a strong indicator of verbal intelligence (Childers et al., 1994; Dunn, 1981; Johnson et al., 1993; Jongsma, 1982), provides a less comprehensive measure of childhood intelligence than can be obtained by alternative tests such as the Wechsler Intelligence Scale for Children-Revised (WISC-R) (Wechsler, 1974). However our findings were very similar to previous findings using the WISC-R (Breslau et al., 2006), which points to the robustness of the PPVT-R as a measure of IQ at least for the purpose of this study. A second and related limitation is that we were only able to use a single and general aspect of neurocognitive performance, verbal ability. Military studies have shown the importance of using more specific measures of neurocognitive performance, including non-verbal measures such as visual-spatial memory, when testing for an association with PTSD (Gilbertson et al., 2006; Marx et al., 2009). Therefore, although our results are supported by military studies which found a relationship between a general construct of cognitive ability (Kremen et al., 2007; Macklin et al., 1998) and verbal memory (Gilbertson et al., 2006) with PTSD, future studies with the capacity to test a wider range of neurocognitive performance measures are needed to show what specific aspects of both verbal and non-verbal abilities are related to the symptoms of trauma. A third limitation, common to many longitudinal birth cohort studies is our considerable loss to follow-up. Results from our attrition analysis found that attrition was biased towards children of lower cognitive ability, this is likely to have led us to underestimate the true effect size. Thus, had these individuals been included in the study it is very unlikely that the magnitude or the significance of the association would have reduced. The inverse probability

weighting analysis revealed very similar results when comparing the lowest and highest functioning quintiles and importantly the gender interaction test was significant. We are aware of the limitations in the use of inverse probability weights in adequately dealing with loss to follow-up. However, given that this analysis produced similar results and given also that we disproportionately lost individuals of lower cognitive ability, it is likely that the relationship would have been found at a similar or greater strength had we collected PTSD data at the 21 year follow-up on all individuals with a PPVT-R score.

Our findings suggest that lower early childhood verbal ability may reduce the capacity of females to cope with trauma. If our results are replicated in future studies, we will have identified a gender-specific risk factor which may explain part of the increased risk of PTSD found to occur in females. In conclusion, more studies with the capacity to test for gender-specific responses to psychopathology, and which employ different measures of neurocognitive performance collected at different stages of development, are needed to further explore what appears to be a dynamic relationship between cognitive ability and psychopathology.

Conflict of interest

All authors declare no conflicts of interest.

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Appendix

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Chapter 8 - Discussion

This chapter discusses the major findings in relation to their contribution to scientific knowledge and their potential for prevention. The overall limitations of the current work are also discussed, along with ideas for future research into life course determinants of psychopathology. For specific technical/critical discussion of findings of each paper (e.g., secondary findings, null findings, the importance of covariables, effect sizes, sensitivity analyses, statistical tests) and limitations, please refer to the corresponding chapter.

Major findings

Fetal development and psychopathology

A major aim of the current work was to contribute to knowledge about the relationship between fetal development and later life psychopathology and in particular assess the latter with more specific psychiatric outcomes. Lower birth weight (adjusted for GA and gender) increased the risk of PTSD and comorbid generalized anxiety disorder and major depressive disorder (GAD+MDD), with the former association remaining when restricting the sample to those exposed to trauma. Birth weight did not predict phobias, panic disorders, GAD or discrete GAD or MDD (i.e., GAD exclusive of MDD and vice versa). Furthermore, birth weight did not predict MDD comorbid with other anxiety disorders. These findings suggest that IUGR may cause permanent alterations to developing stress regulatory systems during fetal growth, leaving the individual at greater risk of specific disorders in young adult life.

Previous studies in this area have tended to focus on broad constructs of psychological or behavior problems (103, 107, 108, 115, 116, 118), groups of combined psychiatric disorders

(112, 119), or individual diagnoses without consideration for confounding by highly related diagnoses (110, 113, 122). If replicated, the current work could lead to a clearer understanding of how IUGR impacts specific mental health disorders and their co-occurrence.

The considerable overlap between the diagnoses of MDD and GAD was discussed in chapter two (63). PTSD also shows considerable comorbidity with MDD and GAD (311), with MDD and GAD thought to play significant roles in the development of PTSD (312, 313). Further, the factor structure analysis suggests that PTSD symptoms demonstrate a strong general distress/negative affectivity component, and may be more rightly grouped along with MDD, GAD and dysthymic disorders under the label of distress disorders (62). Some have pointed out that this relationship may be artifactual and proposed a greater emphasis on symptoms of active avoidance as one solution (314). However, the emphasis on symptoms of negative affect has actually increased under the DSM-V PTSD definition (7), and regardless of the nosological debate, PTSD, MDD and GAD as currently conceptualized will continue to exhibit high comorbidity with the result being that the role each plays in the development and course of the other will receive considerable research attention. The current work suggests that these related disorders, jointly characterised by distress/negative affectivity, appear to share a common etiology related to lower birth weight, but this is not shared by disorders characterised by fear.

It is possible a biological mechanism occurring *in utero* accounts for the associations we found. Chapter two outlined the case that IUGR may be indicative of altered development, which includes permanent reprogramming of the offspring HPA axis that leaves the individual more susceptible to later psychopathology (17). While animal models lack the ability to differentiate behaviours by specific characteristics of human disorders, human

biological studies somewhat support the idea that HPA activity is differently related to specific psychiatric disorders, as studies have found that HPA dysregulation is more strongly associated with anhedonia and distress (characteristic of MDD, GAD and PTSD) than anxious arousal (characteristic of phobias and panic) (315, 316). These studies suggest that anhedonia and distress may be associated with chronic HPA dysregulation, while anxious arousal could be associated with more temporal elevations in HPA activity. Studies have also found that the increased HPA functioning associated with MDD patients compared with controls is due to (317), or is higher among (318), those with comorbid anxiety disorders, suggesting that the combination of MDD and GAD symptoms, rather than either alone, is relevant to HPA dysregulation.

With regard to PTSD, several meta-analyses suggest that a relationship with HPA dysregulation has not been sufficiently demonstrated (319-321). Curiously, the most replicated finding is that PTSD is associated with lower cortisol levels (319, 322), which is somewhat unexpected, and may be explained specifically by symptoms of emotional numbing which are unrelated to depression (322, 323). In addition, PTSD involves all three components of anxious arousal, dysphoria (which includes anhedonia) and non-specific distress/negative affectivity (314); with the components which feature most prominently differing greatly across patients and changing across the course of the disorder (324, 325); and with these components in addition to emotional numbing found differently associated with HPA activity (315, 316, 323). These dynamics, in addition to the numerous confounding factors which impact the expression of PTSD (e.g., levels of social support, cognitive appraisal of the trauma and genetic factors), may explain the inconsistent results regarding PTSD and HPA activity (326). Considering the complexity of the disorder and its presentation, future research aiming to characterise PTSD with biological indicators should do so in the context of a clearly formulated scientific question (320).

Lastly, effect sizes were small, and accounting for a number of covariates does not preclude the possibility of further residual environmental, familial and/or genetic confounding. Conversely, it could be argued that the measure of IUGR (birth weight adjusted for GA) is too crude to detect meaningful effect sizes, or that effect modifiers, which have been ignored by the majority of studies, play a central role in the relationship. If more complex specification of IUGR is indeed necessary to correctly identify associations, the current findings may be helpful in suggesting that the impact of IUGR on later psychopathology may be specific to psychiatric disorders characterised by distress/negative affectivity. Future research should aim to demonstrate clear associations between improved measures of fetal development and these specific psychiatric disorders, which may be stronger in certain subgroups, and attempt to demonstrate mediation by reliable alterations in underlying biological processes.

Prenatal maternal psychopathology and offspring behaviour problems

The current work aimed to elucidate an expanded conceptualization of maternal prenatal psychopathology, derived as trajectories of depression, anxiety and stress across multiple time-points from pregnancy to child age five years, and to assess the differing impact of these empirical trajectories on offspring psychopathology. The main objectives of the current work were to test if prenatal psychopathology more strongly predicted offspring behavior problems during adolescence and adulthood, when compared with trajectories of postnatal psychopathology, after accounting for a wide range of confounding factors operating before and after pregnancy. At 14 years, high levels of maternal prenatal psychopathology predicted internalizing behavior problems when compared with all but one other trajectory, and at 21 years, maternal prenatal psychopathology predicted offspring internalizing and externalizing behaviour problems and depressive symptoms. Aside from one group with ongoing

psychopathology, it is notable that in neither analysis was there an association with adult offspring mental health in groups exposed to maternal depressive, anxious and stress symptoms only during postnatal development, which suggests a 'fetal programming' mechanism may be responsible for the association.

These findings make two major contributions to the related field of research. Firstly, these findings clearly indicate that this association is not limited to early development, but is present among adolescents and young adults. Previous broad-scale birth cohort studies assessing the importance of prenatal psychopathology on offspring development have been limited to assessments in childhood, with the only available findings among adolescence coming from the same high-quality but small sample (152, 155, 156, 159), and with little data available for young adults (327). Practically, this finding increases the significance of the exposure as one which has a lasting negative impact on offspring psychopathology. Secondly, our analytical technique allowed symptoms of depression, anxiety and stress to co-vary across time, and showed that the three constructs expressed together. Thus, these peer-reviewed findings further support calls to consider a fuller range of maternal prenatal and postnatal psychopathology, to improve the well-being of mothers during pregnancy and that of their offspring (160-162).

As outlined in chapter two, we accounted for a number of alternative processes which may have explained the impact of certain trajectories of maternal psychopathology on offspring behaviour problems. While these confounding factors were found to explain the relationship between postnatal trajectories and behaviour problems among the adolescent sample, they did not to explain the impact of prenatal psychopathology. Thus, it may be possible that a biological mechanism operating *in utero,* whereby the increased maternal stress hormones permanently alter the developing fetal HPA axis (see chapter two), is responsible for the

association found (141, 149, 189). The current work was unable to directly account for genetic continuity, and it is possible that part of the association identified is due to genetic inheritance rather than fetal programming. In addition, due to the nature of the categorical predictor variables employed, the analyses were unable to assess for important moderating effects such as gender and child maltreatment, both shown to moderate the relationship between prenatal psychopathology and offspring developmental outcomes (158, 159, 189, 328).

The effects of prenatal psychopathology on later life are moderate in magnitude and may be explainable by residual confounding. However, the relationship is backed by convincing biological evidence, and is found to have far stronger effects when moderated by other risks (159). Measured effects are potentially attenuated by inadequately measured subjective maternal symptoms, and future research with greater capacity is needed to contribute to our understanding of this association. The current work strongly supports the empirical basis of the relationship in a number of ways. The statistical methodology allowed us to more clearly isolate high levels of multiple constructs of psychopathology across time, finding maternal prenatal but not postnatal symptoms consistently predicted behaviour problems in adolescence and adulthood. We did not however find evidence indicating that the association was stronger with advanced offspring age, which we may have expected under the DOHaD hypothesis, as a major theoretical tenant of the DOHaD hypothesis is that early insults affect later health because as age takes an impact on body systems, earlier stresses start to have a greater impact (30, 36, 37). Lastly, as the potential biological mechanism shares some similarities with that of the relationship between fetal development and offspring psychopathology, future studies should assess specific psychiatric outcomes to see if the impact is greater on ‘distress’ disorders, in addition to following the approach to specifying prenatal psychopathology established in the current work.

Stress and illness during pregnancy and offspring psychotic experiences

The third aim of this study was to investigate the neurodevelopmental model of schizophrenia, by assessing whether two prenatal risks predicted psychotic experiences in later life, and how these relationships were influenced by related risk factors in early postnatal life and childhood. The methodologies were novel and designed in accordance with the latest understanding of the neurodevelopmental pathways to schizophrenia, incorporating a continuous dimension of positive psychotic experiences as the outcome, and formal tests of moderation and mediation (82, 199). Application of these methods has helped identify premorbid behavioural abnormalities as representing the early neurodevelopmental sequelae of exposure to prenatal stressful life events, which results in a greater risk of psychotic experiences as the subject ages. Similar evidence for mediation of prenatal insults on later schizophrenia via early abnormal development has been found by investigations into prenatal infection (98, 99). Findings from the second objective suggested that maternal prenatal vaginal infection increased the risk of later positive psychotic experiences in offspring via an increased risk of infant illness susceptibility. This was a novel finding, and while we have not accounted for familial susceptibility to infections (214), suggests the relationship between prenatal infection and schizophrenia requires greater scrutiny.

Collectively, these findings have made a substantive contribution to our understanding of the etiology of the symptomatology underlying psychotic disorders including schizophrenia. The impact of prenatal stressful life events on psychotic experiences may manifest early as behavioural abnormalities. This adds to the existing knowledge by identifying intervening factors which can be modified via early intervention. Childhood behaviour was not found to moderate the effect of prenatal stress on psychotic experiences. This is inconsistent with the suggestion that premorbid developmental abnormalities represent the early and inevitable

manifestation of a genetic risk to schizophrenia development, capable of moderating the impact of environmental exposures on schizophrenia (194). As to prenatal infection, the current work was the first to account for both prenatal infections and early postnatal illness in the prediction of psychosis, thereby suggesting that early postnatal infections increase the risk for later psychotic experiences, while prenatal vaginal infection may be related to psychotic experiences via its contribution to postnatal illness. This has implications for the proposed mechanism, as it suggests that prenatal infection may not directly impact on fetal neurodevelopment, but instead has the potential to be transmitted to the offspring *in utero*, causing illness susceptibility in the first few months of postnatal life (perhaps via congenital infection), which in turn predicts psychotic experiences (200, 329).

These studies included major methodological novelty by employing SEM to construct an empirical multi-dimensional representation of positive symptoms of psychosis using questions drawn from a semi-structured interview. Though with some notable differences, mostly pertaining to the omission of grandiosity and multiple indicators of paranormal beliefs, the three factors identified in the current work were similar to the three principal factors identified and replicated by Wigman (91, 299). Wigman however, unlike the current work and a recent study which employed a wider array of psychotic symptoms (300), did not impose a general construct across the highly correlated psychotic subdimensions.

It may be worth noting some aspects of the bifactor model as it relates to the psychotic experiences present in the sample. When exploring the general structure of the three factors using bifactor analysis, the general factor was found to directly explain the variance in the six hallucinations items, and these items also had the strongest loadings. From this it was inferred that hallucinations represent the 'bulk' of the general positive symptoms of psychosis factor, and that a purely hallucinations dimension does not exist independently of delusions in the MUSP sample. Regarding the specific group factors, due to the high factor loadings and the

association with social phobia (see supplementary results in chapter 6), it is likely that the paranoia/reference factor represents a substantive subdimension of young people with differing levels of paranoid and referentially distorted thinking without hallucinations (330). It is likely that the thought interference factor simply represents 'nuisance variance' resulting from semantic similarity among the items (301), as the three items on this factor with loadings above 0.2 all refer to 'mind reading' of sorts.

These findings need to be understood with regard to a major consideration relevant to future research. While the risk factors included in the current work have received considerable attention with regards to their impact on psychotic disorders, they are in fact non-specific risks for a range of non-psychotic disorders and developmental outcomes (199). While the current work has contributed to this line of research by identifying factors on the causal pathway to the development of psychosis, our research question was specific to risk factors such as prenatal vaginal infection and childhood behaviour problems. In addition to assessing multiple outcomes, future studies should investigate a greater range of potential moderating, mediating and confounding factors such as genetic factors, not least more specific prenatal infections and developmental abnormalities such as neurocognition and motor development.

Gender-specific response to traumatic stress

The final aim of the study was to expand knowledge on the sources of the female increased risk to PTSD by assessing the impact of non-sexual assault and lower cognitive ability on the gender-specific risk to PTSD. Our first objective was to investigate gender differences in PTSD resulting from certain types of trauma exposure. The current work provides the strongest evidence yet that physical assault is unique among the trauma events in disproportionately impacting on female PTSD risk. A highly significant second order interaction indicated a non-proportional relationship between trauma type and the level of

PTSD, which was also moderated by gender. The estimates indicate that this non-proportionality results from the differentially increased odds of both levels of the outcome in females compared with males exposed to physical assault, a substantively similar finding as found previously using a simpler model (223). Lastly, while exposure to molestation/rape was far more prevalent among women, and most strongly associated with developing partial or full PTSD and full PTSD only in both males and females, attributable risk analysis suggested physical assault was responsible for far more of the increased absolute risk of PTSD found in women, than sexual assault. Thus, the prevalence of these two traumatic exposures by gender is the reverse of the impact they have on the absolute rates of PTSD by gender, strongly suggesting that physical assault is a major cause of the increased PTSD risk in females.

The strength of the effect seems to leave little doubt about the importance of the association. However, it is suggested that the strongly increased female risk to partial and full PTSD, is at least in part, simply reflective of how poorly trauma concerning non-sexual assault is operationalized in epidemiological surveys (discussed in chapter 2). This is based on evidence that the experience of rape and military combat do not produce similarly strong discrepancies between males and females (146, 331, 332). Nonetheless, the strength of the increased risk in females, even after accounting for prior behaviour problems and multiple traumatic exposure, requires explanation. While there is evidence that men and women react to stressful situations differently (227), the true causes of the observed gender differences cannot be properly tested until the traumatic events are defined with greater specificity (219, 227). Lastly, it is interesting to note that the effect is only slightly weaker when including subclinical levels of PTSD in the outcome. Considering that the PTSD diagnosis is considered restrictive when diagnosing young people (55, 333), the absolute contribution to female traumatic stress following physical assault may be even larger.

In carrying out the second objective by investigating gender differences in the impact of childhood cognitive ability on PTSD, the current work provides the first evidence that the increased risk of anxiety and depression among females with lower cognitive ability or intelligence in early development (229-232) is also relevant to PTSD. Even after controlling for a range of important trauma-related and sociodemographic factors, females scoring in the lowest quintile of verbal ability at age five years had an almost four fold increased risk of later PTSD compared with those scoring in the highest quintile. Further, as birth weight did not account for this association, this suggests that lower cognitive ability may impair females ability to process and cope with traumatic experiences (234, 236, 238, 248), instead of simply representing a general brain vulnerability due to abnormal fetal development (245). If further research replicated these findings, cognitive ability may represent a significant contributor to the female increased risk of PTSD, a risk factor that some have suggested may be amenable to prevention programs (232).

General Strengths

The broad range of measures and large number of participants included in the Mater University Study of Pregnancy (MUSP) are the most obvious strengths of the current work, allowing researchers to test specific directional hypothesis across a number of years of development, while also accounting for a number of alternative processes including mediated and moderated effects. Despite the considerable attrition associated with certain measurement instruments and long periods between some measurements, the MUSP is unique worldwide in being able to study the development of psychopathology over the first 21 years of life in such a rich context. A great strength of the MUSP is that all data have been measured prospectively, making it possible to establish temporality and limit recall bias. The MUSP has used indices and existing validated scales, such as The Youth Self-Report, the Delusions-

Symptoms-States Inventory and the Composite International Diagnostic Interview (251). Repeated measurements have been used at different follow-ups, making it possible to track patterns in the mother's and child's psychopathology across time (251). Since its conception in the early 1980s, the MUSP has contributed a wealth of knowledge to our understanding of life course determinants of psychopathology, with more recent publications investigating relationships with childhood maltreatment (334), substance abuse (108), poverty (335), relationships (336), psychotic experiences (337), and suicidal behaviours (338).

A major goal of the author throughout the current work was to apply advanced latent and/or longitudinal statistical techniques to the MUSP data, in efforts to increase the potential of the data to answer complex questions, an approach the author later felt was supported by the emphasis given to such techniques at the Australasian Epidemiological Association annual conference in Brisbane, 2013. The theoretical strengths and importance of these advanced techniques to life course epidemiology was described in chapter three. Briefly, the LCGA approach resulted in the identification of a number of discontinuous, empirical trajectories of maternal psychopathology across five years, leading to a clear relationship between prenatal symptoms and offspring behaviour problems at two distinct developmental periods (chapter five). In addition, SEM was applied to construct the first latent bifactor model of psychotic experiences (300) to be used in a longitudinal risk factor study, and included formal tests of moderation and mediation (chapter 6).

General Limitations

Despite the considerable strengths of the current work, there are five major limitations which concern the internal and external validity of the main findings. The most salient is the considerable loss to follow-up in the MUSP. Attrition is not easy to describe as it does not simply reflect an expected cumulative loss as the follow-ups progress, but varies depending

on the proforma used (described in further detail in the studies). For example, while 53% (*n* = 3,843) of the offspring participants at the 21 year follow-up completed the Centre for Epidemiologic Studies-Depression scale (108), only 35.7% (*n* = 2,563) completed the CIDI-Auto interview (251). Such a large loss to follow-up raises concerns about the validity of the study findings, particularly if the probability of loss is related to the exposure or outcome (253). In consequence of having a complete dataset at baseline, it has been possible to compare the baseline factors between participants who have been lost to follow-up with the remaining sample. This makes both the simple attrition analysis and the more sophisticated multivariate multiple imputations method possible, for which the strengths and weaknesses of each approach were outlined in the methodology.

Second, when compared with other cohort studies (e.g., ALSPAC in the UK and the RAINE study in Western Australia) the MUSP has relatively long gaps between the follow-up periods (251). For some models this has resulted in a lack of cognitive, behavioral, anthropometric and general health and lifestyle factors during key developmental periods such as the infant and juvenile period. A more detailed examination of childhood developmental factors requires growth measurements during infancy and childhood, with the juvenile period of growth understood to occur between ages 3 and 11 (339).

Third, at the time of completing this thesis the ascertainment of blood samples among the offspring cohort remains underway. The MUSP will soon have the capacity to include genetic information in its analyses (340). However, over the duration of this thesis it was not possible to explore the involvement of genetic factors in the tested hypotheses. The lack of epigenetic and biological measures meant the biological mechanisms proposed to mediate the relationships between the risk and outcome could not be demonstrated. The potential of such information to future studies is discussed in the subsequent section.

Fourth, the large scale of the MUSP project meant that feasibility played a major role in the selection of measurement instruments. This could result in either the use of high quality measures on a subsample of participants, as exemplified by the semi-structured psychiatric interview at 21 years (CIDI-Auto), or the use of a less reliable measure on all respondents, exemplified by the numerous self-report measures used throughout the course of the MUSP. Of particular concern to the current work were measures including prenatal vaginal infection, infant illness susceptibility, the use of PPVT-R as a measure of cognitive ability, and the lack of information on the father's mental illness history. The strengths and weaknesses of these many variables were discussed in the relevant papers.

Lastly, observational epidemiology as a scientific discipline has strengths and weaknesses. As the MUSP satisfies many of the basic and age-old requirements for reducing systematic bias in observational studies, including prospective measures, measurements taken from medical records, the use of validated instruments and larger sample size (253), the main concern with regard to the current work is residual confounding. Methodologies specifically designed to deal with concerns raised by confounding, such as twin/sibling analyses or assisted reproductive technologies studies, are needed to support findings from general populations. While in theory randomised controlled trials (RCTs) offer a solution to confounding by randomising the exposure, in practice RCTs have no place in the current work for ethical reasons. Thus, while causality can't be demonstrated by observational epidemiological methods, confidence in the predictive utility of life course risk factors for psychopathology will be driven by methodological and statistical innovations within observational epidemiology, and such innovation should be prioritised.

Future research

Researchers concerned with the primary prevention of psychopathology face the reality that the risk factors they study are not suitable for RCTs. The result is that the highest level of evidence is unattainable for prevention factors, with the implication that policy decisions favor intervention and treatment, which can be evaluated by RCTs. Thus, as prevention research appears limited to observational study designs, a discussion about how such evidence may be strengthened in future research concerning the early life course determinants of psychopathology is warranted. The following three points are discussed separately for clarity, but are interrelated.

Firstly, DNA is likely to play a prominent role in the future of observational epidemiology. The main aim of genome-wide association studies (GWAS) has been to discover which common genetic polymorphisms, most usually single nucleotide polymorphisms (SNPs), are associated with common human disorders (341). However, GWAS data can also be used to statistically account for the proportion of the outcome explained by the SNPs, resulting in a heritability estimate which unlike those ascertained via twin studies is not confounded by shared environment (342, 343). Though only considered a lower bound estimate of narrow-sense heritability (342), the ability to account for SNPs may produce more reliable estimates between the environmental exposure and outcome, particularly if the genetic influences are somehow related to the exposure.

Secondly, a greater emphasis should be placed on demonstrating the biological mechanisms thought to mediate the epidemiological associations. In addition to the biological markers of implicated regulatory systems, the role of the proposed epigenetic mechanisms, thought to respond to the environmental exposure or the G × E interaction and permanently alter the expression of such systems, could be observed (343). Regarding *in utero* exposures, this will

include a greater focus on how maternal insults are transmitted to the fetus (141), for which recent evidence suggests the placenta may play a central role (129). On a related note, a recent meta-analysis concerning the neurodevelopment of schizophrenia points out that in addition to obtaining biological measures, greater effort is required to demonstrate their roles within study designs incorporating formal tests of mediation (199).

Lastly, by recognising the importance of moderating and mediation effects among environmental and genetic factors, comes the implicit recognition that these risk factors do not act in isolation, but are complexly interrelated with later disease risk (344). Furthermore, these risk factors are not related to discrete or specific psychiatric disorders in later life, but are instead predictive of a range of neurodevelopmental outcomes, with their role in specific disorders representing one point in a complex causal pathway (202). Thus while in reality the data at hand will necessitate a reductionist approach to the problem, as exemplified by the testing of a number of individual directional hypotheses in the current work, future research should be designed with the capacity to better account for the multifaceted causal pathways among a number of exposures and outcomes (344).

Implications for primary prevention

Currently, prevention efforts in reducing community mental illness remain in need of a stronger research base. While the findings of the current work do support the potential for prevention to address mental health problems in Australia, this section focuses on providing some practical implications of the current findings to prevention approaches. Importantly, at this stage these suggestions are merely illustrative of practical prevention strategies informed by research in this thesis. It is necessary to once again stress that this research was based on observational study designs, for which replication by high-quality studies driven by clear hypothesis would be necessary before investing in such strategies could be considered viable.

- Obstetric medicine and public health programs could place a greater emphasis on the detection and elimination of prenatal teratogens, in addition to raising awareness of 'behavioural' risk factors (i.e., under nutrition, smoking, teen pregnancy, etc) associated with intrauterine growth restriction.

- Existing Federal Government initiatives aimed at the screening and treatment of perinatal depression (12) need to address anxiety and stress symptoms in efforts to improve treatment and reduce negative long term outcomes for mother and child (161, 345).

- Exposure to negative life events should be assessed during pregnancy and additional social support could be provided to reduce the impact of such events on maternal mental health.

- Infectious disease control programs should place greater emphasis on the prevention of common infections during pregnancy and early infancy.

- Programs and laws in place to protect women from physical violence should be strengthened, and greater public awareness raised of the circumstances which may drive the strong increase in psychopathology among women (i.e., intimate partner violence).

Conclusion

The current work contributes a number of substantive findings to the existing body of work related to early life course determinants of psychopathology in young adults, and demonstrates how advanced statistical techniques can be applied to epidemiological methods in an effort to derive clearer relationships. The current work found sub-optimal fetal growth

to be predictive of later offspring psychopathology, suggesting the relationship is specific to psychiatric disorders characterised by negative affectivity. The association between maternal prenatal psychopathology and offspring psychopathology was also confirmed, and established to impact offspring's psychopathology at later stages of development than previously thought. The work also strengthens empirical support for the neurodevelopmental model of schizophrenia by demonstrating the importance of early infant illness susceptibility to the relationship between prenatal infection and psychotic experiences, and childhood behaviour problems to the relationship between prenatal stressful life events and psychotic experiences. Lastly, lower cognitive ability and exposure to non-sexual physical assault were found to be two factors which drive the increased female risk to PTSD.

With regard to prevention programs, while proposing further research is needed to inform effective programs, the findings in this work strengthen support for the feasibility of preventive approaches to psychopathology. While human programming studies with the capacity to examine epigenetic changes hold promise for reducing disease burdens, epigenetic mechanisms are likely complicated, with the development of effective interventions taking time and better suited to early interventions in individuals who already exhibit vulnerable phenotypes (346). Thus focusing on firstly understanding and then eliminating environmental factors may be the more viable option in the short term. Importantly however, this is not to advocate the simple adoption of universal prevention programs, which by failing to target the vulnerable subgroups may ultimately be judged ineffective (163), with detrimental consequences to the perceived viability of future prevention programs. Thus, research should aim to identify groups within which specialized prevention will be shown effective, with the later expansion of primary prevention approaches gaining approval from earlier successes.

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Appendix 1: Definitions and prevalence of psychiatric disorders

Table 1 DSM-IV definitions of psychiatric disorders under study

Anxiety disorders:

Post-traumatic stress disorders (PTSD) is based on the exposure to a traumatic event which involved actual or threatened death or serious injury or threat to the individual or others, which aroused a severe affective response characterized by fear, helplessness or horror in the individual. Several conditions must be met to diagnose an individual with PTSD including: persistent and intrusive reexperiences of the event, persistent avoidance of stimuli associated with the trauma, persistent symptoms of arousal not present before exposure to the event, symptoms lasting longer than one month, and disturbances which cause impaired functioning in important areas of the individual's life.

Social phobia is defined as a marked and persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or to the possible scrutiny of others. To gain a diagnosis, the individual must be aware that the anxiety response is excessive and leads them to either avoid the situation or endure it with much distress or functional impairment.

Specific phobias is defined as a marked and persistent fear of clearly discernible, circumscribed objects or situations. Exposure to the phobic stimulus almost invariably provokes an immediate anxiety response. To gain a diagnosis, the individual must be aware that the anxiety response is excessive and leads them to either avoid the situation or endure it with much distress or functional impairment.

Panic Disorders (PD) with and without Agoraphobia requires the presence of recurrent, unexpected Panic Attacks followed by at least one month of persistent concern about having another Panic Attack, worry about the possible implications or consequences of the Panic Attacks or a significant behavioral change related to the attacks. A Panic Attack is a discrete period of intense fear or discomfort in the absence of real danger which is accompanied by 4 of 13 somatic or cognitive symptoms (not described here). People with Panic Disorder may also experience Agoraphobia, defined as anxiety about being in places or situations from which escape might be difficult (or embarrassing) or in which help may not be available in the event of having a Panic Attack.

Generalised anxiety disorders (GAD) is defined as excessive anxiety and worry (apprehensive expectation) occurring for a majority of days during at least a six month period about a number of events or activities. Because anxiety and worry are normal human behaviours, two additional conditions must be met to distinguish trait or normal anxiety from GAD. Firstly, an individual must experience three of the following six somatic symptoms: restlessness or feeling on edge, being easily fatigued, difficulty concentrating, irritability, muscle tension, and sleep disturbance. Secondly, the anxiety must be uncontrollable, causing impaired functioning in important areas of the individual's life.

Affective disorders:

Major Depressive Disorders (MDD) is defined as a clinical course characterized by one or more Major Depressive Episodes, without a history of manic, mixed, or hypomanic episodes. A Major Depressive Episode is a period of at least 2 weeks during which there is either depressed mood or the loss of interest or pleasure in nearly all activities. To gain a diagnosis an individual must also experience at least four of the following: change in appetite or weight, sleep, and psychomotor activity; decreased energy; feelings of worthlessness or guilt; difficulty thinking, concentrating or making decisions; or recurrent thoughts of death or suicidal ideation, plans, or attempts. The symptoms must have newly developed or worsened compared to the person's preepisode status and be persistent for most of the day, nearly every day, for two consecutive weeks. The episode must be accompanied by clinically significant distress or impairment.

Dysthymic Disorders is defined as chronically depressed mood that occurs for most of the day more days than not for at least 2 years, in which at least two of the following symptoms is present: poor appetite or overeating; insomnia or hypersomnia, low energy or fatigue, low self-esteem, poor concentration or difficulty making decisions, and feelings of hopelessness. The symptoms must cause clinically significant distress or impairment.

Psychotic disorders:

Schizophrenia is a disorder that lasts for at least 6 months and includes at least 1 month of active-phase symptoms, in which 2 or more schizophrenia related symptoms are present and are associated with marked social or occupational dysfunction. The symptoms fall into two broad categories: positive symptoms which reflect an excess or distortion of normal functions including delusions, hallucinations, disorganized speech and grossly disorganized or catatonic behaviour; and negative symptoms which reflect and diminution or loss of normal functions including affective flattening, alogia (fluency and productivity of thought and speech) and avolition (initiation of goal-directed behaviour).

Note: A diagnosis may only be given if symptoms do not result from substance abuse, medication or another medical condition, and in the case of anxiety disorders symptoms must occur in isolation of an actual threat.

Table 2 12-month prevalence of ICD-10 affective and anxiety disorders in Australia by gender: 1997 and 2007

	1997 (%)			2007 (%)		
	Male	Female	Persons	Male	Female	Persons
Panic Disorder	0.6	2.0	1.3	2.3	2.9	2.6
Agoraphobia	0.7	1.5	1.1	2.1	3.5	2.8
Social Phobia	2.4	3.0	2.7	3.8	5.7	4.7
GAD[1]	2.4	3.7	3.1	2.0	3.5	2.7
OCD[2]	0.3	0.4	0.4	1.6	2.2	1.9
PTSD[3]	2.3	4.2	3.3	4.6	8.3	6.4
Total Anxiety Disorders	**7.1**	**12.1**	**9.7**	**10.8**	**17.9**	**14.4**
MDE[4]	3.4	6.8	5.1	3.1	5.1	4.1
Dysthymia	1.0	1.3	1.1	1.0	1.5	1.3
BAD[5]	-	-	-	1.8	1.7	1.8
Total Affective Disorders	**4.2**	**7.4**	**5.8**	**5.3**	**7.1**	**6.2**

Note: In 1997 the estimates of BAD were low and not included (and were also not included in the total affective disorders estimate).
1 Generalised Anxiety Disorder; 2 Obsessive Compulsive Disorders; 3 Post-Traumatic Stress Disorder; 4 Major Depressive Episode; 5 Bipolar Affective disorder.

Appendix 2: Descriptive statistics of MUSP instruments/variables.

Figure 1: Flow chart of MUSP recruitment and participation including samples sizes

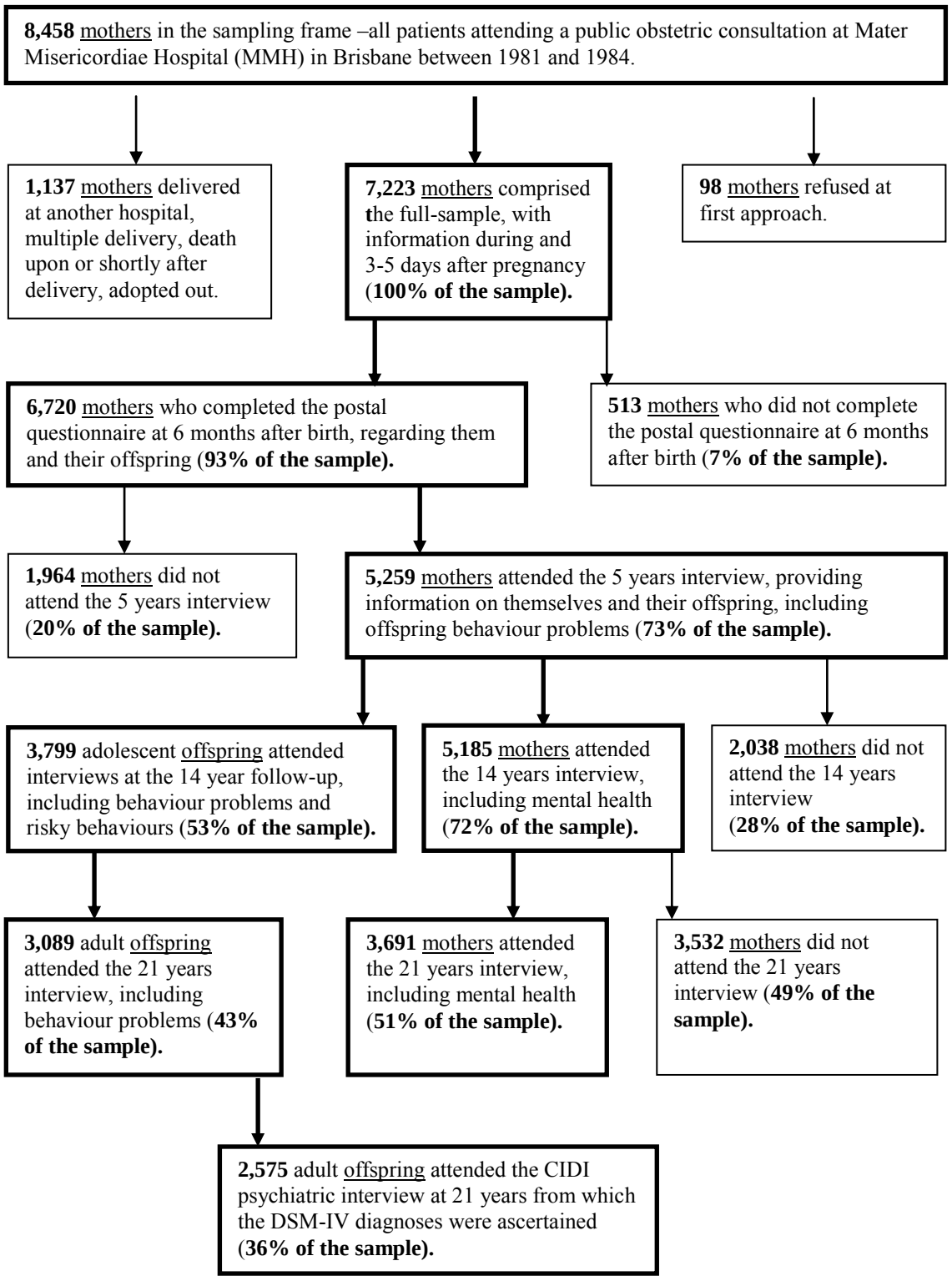

Table 3 Time period, informant and sample size by MUSP variables used in the current work

	Phases of the MUSP					
	Pregnancy	***Birth***	***6 months***	***5 yrs***	***14 yrs***	***21 yrs***
Mothers (*n*)	*7,223*	*7,223*	*6,720*	*5,234*	*5,185*	*3,691*
Offspring (*n*)	*7,223*	*7,223*	*6,720*	*5,259*	*5,172*	*3,809*
Offspring psychopathology						
Psychiatric diagnosis *						C
Depressive symptoms						C
Behaviour problems				MC	C	C
Maternal psychopathology						
Anxiety and depression symptoms	M	M	M	M	M	M
Subjective stress symptoms	M	M	M	M		
Stressful life events		M		M		
Paternal psychopathology						
Seen doctor for mental problem				MF	MF	MF
Prenatal risk factors						
Birth weight z-score		MED				
Prenatal infection	M					
Prenatal smoking	M	M				
Prenatal alcohol	M	M				
Apgar score		MED				
Forced induction of labour		MED				
Baby required specialist attention		M				
Pre-eclampsia		M				
Early developmental risk factors						
Offspring cognitive ability				C		
Offspring illness susceptibility			M			
Confounders						
Income	M					C
Education	M					C
Maternal age	M					
Parity	M					
Maternal child rearing			M			
Maternal relationship status	M					
Maternal relationship quality		M				
Offspring gender		MED				

Note: * Psychiatric diagnoses were ascertained for a subsample of offspring at 21 years (*n* = 2,251), which included information on exposure to traumatic events.

M = maternal report on herself; MC = maternal report on child; MF = maternal report on father; C = child report on self; MED = taken from medical records.

Table 4 MUSP summary statistics for categorical variables

Value	Frequency	Percent	Value	Frequency	Percent
Externalising Probs-10%-YASR at 21			Externalising-CBCL- 5 years		
Normal	3495	90.92	Normal	4675	89.29
Case	349	9.08	Case	561	10.71
Missing = 3379			*Missing = 1987*		
Internalising Probs-10%-YASR at 21			Internalising-CBCL- 5 years		
Normal	3463	90.09	Normal	4617	88.26
Case	381	9.91	Case	614	11.74
Missing = 3379			*Missing = 1992*		
Externalising Probs-10%-YASR at 14			Total behaviour problems-CBCL- 5 years		
Normal	4679	90.57	Normal	4857	92.83
10% range	487	9.43	Case	375	7.17
Missing = 2057			*Missing = 1991*		
Internalising Probs-10%-YASR at 14			Depression-10%-CES-D at 21		
Normal	4654	90.09	Normal	3369	
10% range	512	9.91	Case	376	
Missing = 2057			*Missing = 3478*		
5 quintiles of Peabody			Birth weight z-score quintiles		
1 - lowest scoring	863	21.58	1 - Lowest z-score	1455	20.14
2	837	20.93	2	1435	19.87
3	705	17.63	3	1447	20.03
4	806	20.16	4	1442	19.96
5 - highest scoring	788	19.7	5 - Highest z-score	1444	19.99
Missing = 3224					

Note: maternal symptoms of depression, anxiety and stress are summarised in chapter 5. FCV-First Clinic Visit.

Missing is the frequency total subtracted from the baseline sample of 7223.

Table 4 ***continued…***

Value	Frequency	Percent	Value	Frequency	Percent
Maternal stressful life events - at birth			Maternal stressful life events - at child age 5		
0-3	6667	93.13	None to 3	4307	87.77
Four plus	492	6.87	4+	600	12.23
Missing = 64			*Missing = 2316*		
Maternal smoking FCV			Maternal smoking late pregnancy		
Nil smoked	4422	61.79	Nil smoked	4351	60.47
Smoker	2117	29.58	Smoker	1949	27.09
Heavy	617	8.62	Heavy	895	12.44
Missing = 67			*Missing = 28*		
Mat alcohol FCV (stand. drinks)			Maternal alcohol late pregnancy (stand. drinks)		
Nil	3609	50.33	Nil	4655	64.71
>0 - .5 per day	3263	45.51	>0 - .5 per day	2170	30.16
>.5 - 1 per day	174	2.43	>.5 - 1 per day	223	3.1
>1 per day	124	1.73	>1 per day	146	2.03
Missing = 53			*Missing = 29*		
Maternal education at FCV			Family income at FCV		
Post high	1256	17.52	High	2308	34.2
Complete high	4609	64.28	Middle	3709	54.96
Incomplete high	1305	18.2	Low	732	10.85
Missing = 53			*Missing = 474*		
Maternal marital status at FCV			Maternal relationship quality at birth		
Single	736	10.28	Conflict	119	1.67
Living together	844	11.79	Mod adj	689	9.64
Married	5386	75.22	Good adj	5984	83.76
Sep-div-wid	194	2.71	No part	352	4.93
Missing = 63			*Missing = 79*		

Note: maternal symptoms of depression, anxiety and stress are summarised in chapter 5. FCV-First Clinic Visit.

Missing is the frequency total subtracted from the baseline sample of 7223.

Table 4 ***continued…***

	Frequency	Percent		Frequency	Percent
Maternal contact with new born (6 months)			Parity (categorical)		
Contact wanted	6023	85.50	none	2940	40.7
Borderline	469	6.70	one or two	3443	47.67
Contact not wanted	556	7.90	three or more	840	11.63
Partner had mental prob. last 5 years (5 yrs)			Partner had mental prob. last 5 years (14 yrs)		
No	4902	95.54	No	4666	93.85
Yes	229	4.46	Yes	306	6.15
Missing = 2092			*Missing = 2251*		
Partner had mental prob. ever (21 yrs)			Maternal age at birth (categorised)		
No	3318	85.08	≥35	1181	16.35
Yes	582	14.92	20-34	5723	79.23
Missing = 3323			13-19	319	4.42
Offspring gender			Forced induction of labour		
Male	3748	51.89	No	5628	77.92
Female	3475	48.11	Yes	1595	22.08
Diagnosed with preeclampsia while pregnant			Apgar score at 1 minute (<7)		
No	6635	91.86	≥7	5861	84.95
Yes	588	8.14	<7	1038	15.05
			Missing = 324		
Baby required specialist attention at delivery			Vaginal discharge/infection during pregnancy		
Did not happen	5105	71.89	Did not happen	3524	49.51
Yes-but not problem	1429	20.12	Yes-but not problem	2253	31.65
Moderate problem	438	6.17	Moderate problem	1009	14.18
Major problem	129	1.82	Major problem	332	4.66
Missing = 122			*Missing = 105*		

Note: maternal symptoms of depression, anxiety and stress are summerised in chapter 5. FCV-First Clinic Visit.

Missing is the frequency total subtracted from the baseline sample of 7223.

Table 5 MUSP summary statistics for continuous variables

Variable	*n*	Mean	S.D.	Min.	Max.
CES-Depression - 21 yrs	3745	11.22	8.69	0	57
Internalising - 21 yrs	3844	10.72	8.29	0	45
Externalising - 21 yrs	3844	9.44	6.83	0	41
Internalising - 14 yrs	5166	13.55	7.73	0	51
Externalising - 14 yrs	5166	12.92	7.40	0	51
Internalising - 5 yrs	5231	3.76	2.95	0	20
Externalising - 5 yrs	5236	6.04	3.55	0	20
Total behaviour probs. - 5 yrs	5232	4.75	2.66	0	17.58
BWT z-score	7223	0.00	1.00	-3.87	5.65
Peabody	3999	99.43	13.79	40	142
Maternal age - FCV	7223	24.55	5.12	13	46
Maternal parity - FCV	7223	1.067562	1.22237	0	10

Table 6 Life time and 12 month Prevalence of DSM-IV diagnosis in MUSP young adults (*n* = 2,575)

	Life time diagnosis (%)			12 month diagnosis (%)		
	Male	Female	Persons	Male	Female	Persons
PTSD	3.5	9.1	6.3	2.6	6.1	4.4
GAD	2.8	6.0	4.4	1.7	3.0	2.4
Social Phobia	4.5	11.3	7.9	2.1	6.1	4.1
Specific Phobia	6.1	18.5	12.5	4.5	15.8	10.3
Agoraphobia	2.0	5.1	3.5	1.2	3.6	2.5
Panic Disorder	1.6	5.3	3.6	1.1	4.0	2.7
Any Anxiety Disorder	**14.9**	**34.6**	**25.0**	**10.6**	**27.1**	**19.0**
MDD	13.1	26.1	21.5	6.2	12.4	11.0
Dysthymia	1.1	2.1	1.6	0.5	0.7	0.6
Any Affective Disorder	**14.9**	**28.0**	**21.5**	**7.5**	**13.9**	**10.7**
Any psychotic disorder	**1.1**	**1.7**	**1.4**	**0.5**	**1.0**	**0.7**

Notes: Due to small numbers of severe and recurrent depression, MDD was not specified by severity or recurrence in the current work; a diagnosis of agoraphobia was only given if the individual did not also have panic disorders; any psychotic disorders included a number of psychotic disorders listed in chapter 6.

Table 7 Items used in the internalising scale at three time points

Internalising items	5-year mother CBCL (*n*=5,231)	14-year offspring YSR (*n*=5,166)	21-year offspring YASR (*n*=3,844)
Anxious/depressed subscale			
Feels lonely		+	+
Cry a lot	+	+	+
Try to hurt/kill self		+	
Afraid of doing something bad		+	+
Feel have to be perfect		+	+
Feel no one loves them		+	+
Feel others out to get them		+	+
Feel worthless or inferior	+	+	+
Nervous or tense	+	+	+
Fearful or anxious	+	+	+
Feel too guilty	+	+	+
Self-conscious/easily embarrassed		+	+
Suspicious		+	
Think about killing self		+	+
Unhappy, sad or depressed		+	+
Worry a lot	+	+	+
Confused or in a fog			+
Too concerned with appearance			+
Worry about relations with opposite sex			+
Withdrawn subscale			
Likes to be alone	+	+	+
Refuse to talk	+	+	+
Secretive or keeps things to self		+	+
Shy		+	+
Don't have much energy		+	
Not liked by others	+[a]		+
Trouble making and keeping friends			+
Stares blankly			
Sulks a lot	+		
Withdrawn, doesn't get involved with others	+	+	+
Somatic subscale [b]			
Feel dizzy		+	
Overtired		+	
Aches or pains		+	
Headaches		+	
Nausea, feel sick		+	
Problems with eyes		+	
Rashes or skin problems		+	
Stomach ache/cramps		+	
Vomiting		+	
Number of items in each scale	10	31	24
Cronbach's alpha coefficient	0.76	0.87	0.91

Note: (a) Item collected but not included in the internalising scale at 5 years.
(b) Somatic symptoms were specific to YSR internalising.

Table 8 Items used in the externalising scale at three time points and reliability measures

Internalising items	**5-year mother** CBCL (*n*=5,237)	**14-year offspring** YSR (*n*=5,166)	**21-year offspring** YASR (*n*=3,844)
Aggression subscale			
Argues a lot	+	+	+
Brag, boast		+	+[b]
Mean to others, bullying		+	+
Attention seeking	+	+	+[b]
Destroys own belongings	+	+	
Destroys others belongings	+	+	+[a]
Disobedient at school		+	
Disobedient at home	+		
Jealous of others		+	
Gets in many fights	+	+	+
Physically attacks people		+	+
Screams a lot	+	+	+
Shows off		+	+[b]
Stubborn, sullen or irritable	+	+	+
Mood swings	+	+	+
Threaten to hurt others		+	+
Have a hot temper	+	+	+
Feel others out to get them			+[c]
Doesn't get along with family			+
Get teased a lot			+[b]
Talk too much		+	+[b]
Louder than others		+	+[b]
Teases others a lot		+	+[b]
Doesn't get along with other people			+
Delinquent subscale		+	
Don't feel guilty		+	
Hang around with kids who get in trouble		+	+
Lie or cheat		+	+
Rather be with older kids		+	
Run away from home		+	
Set fires		+	
Steal at home		+	
Steal outside home		+	+
Swear or use dirty language		+	
Cut classes or skip school		+	
Use alcohol or drugs recreationally		+	
Use drugs (other than alcohol) recreationally			+
Drink too much alcohol to get drunk			+
Do things which may cause trouble with law			+
Break rules were I work, study or elsewhere			+
Fail to pay debts, meet financial responsibilities			+
Number of items in each scale	10	31	28
Cronbach's alpha coefficient	0.83	0.88	0.88

Note: (a) In the YASR this item was included in the delinquent subscale.
(b) In the YASR these items were included in a new subscale labelled intrusive behaviours.
(c) In the YASR this item was included in the aggression subscale and the anxious/depressed subscale.

Table 9 CES-D items among MUSP offspring at 21 years

1. Bothered by things which don't bother normally 2. Did not feel like eating: had poor appetite 3. Could not shake off the blues even with help from family or friends 4. Felt just as good as other people 5. Had trouble keeping my mind on what I was doing 6. Felt depressed 7. Felt everything I did was an effort 8. Felt hopeful about the future 9. Thought my life had been a failure 10. Felt fearful	11. Sleep was restless 12. Felt happy 13. Talked less than usual 14. Felt lonely 15. People were unfriendly 16. Enjoyed life 17. Had crying spells 18. Felt sad 19. Felt other people disliked me 20. Could not get 'going'
Total number of respondents = 3,745	*Cronbach's alpha coefficient = 0.88*

Note: items were rated on a frequency scale (less than 1 day/ 1-2 days/ 3-4 days/ 5-7 days).

Table 10 DSSI anxiety and depression items, sample size and reliability in MUSP mothers

DSSI – Depression scale	DSSI - Anxiety scale
1. Been so miserable have had difficulty sleeping. 2. Been depressed without knowing why. 3. Have gone to bed not caring if I woke up. 4. So low in spirit have sat up for ages doing absolutely nothing. 5. The future seems hopeless. 6. Have lost interest in just about everything. 7. So depressed thought of doing away with myself	1. Worried about every little thing. 2. Been breathless or had a pounding heart. 3. Been so worked up I could not sit still. 4. Been so anxious I could not make up my mind about the simplest things. 5. Worrying has kept me awake at night. 6. For no good reason have had feelings of panic. 7. Have had pain or a tense feeling in neck/head
Pregnancy (n = 7,085, α = 0.79); *Birth (n = 7,205,* α = 0.81); *six months (n = 6,693,* α = 0.83); *five years (n = 5,215,* α = 0.86); *14 years (n = 5,172,* α = 0.88);	*Pregnancy (n = 7,089,* α = 0.76); *Birth (n = 7,208,* α = 0.81); *six months (n = 6,693,* α = 0.83); *five years (n = 5,215,* α = 0.84); *14 years (n = 5,170,* α = 0.85);

Note: Responses were on a 5-point scale (all of the time = 5; most of the time = 4; some of the time = 3; rarely = 2; never = 1) and asked in reference to the how respondents felt 'recently'.

Table 11 DAS items among mothers recorded at birth

1. Things between you and your partner are going well?
2. How often do you think of divorce, separation or terminating your relationship?
3. How often do you or your partner leave the house after a fight?
4. Do you find it easy to confide in your partner?
5. Do you ever regret marrying or living with your partner?
6. How often do you and your partner quarrel?
7. How often do you and your partner "get on each other's nerves?"
8. How satisfied are you with your relationship with your partner?

Total number of respondents = 7,114	*Cronbach's alpha coefficient = 0.83*

Appendix 3: CIDI-Auto 2.1interview structure for selected sections

Post-traumatic Stress Disorders

In the CIDI 2.1 subjects were asked to nominate any traumatic events they had experienced from a selection of 11 predefined events, which were collapsed into five categories of trauma type (see paper seven, chapter seven). Regarding the specified (worst) trauma, it was firstly determined if the subjects had an acute reaction to the trauma, namely feeling helpless or horrified. Subjects were then asked a total of 17 questions relating to the experience of three symptoms clusters, re-experiencing, hyperarousal and avoidance, of which positive responses $\geq$ 1 of 5, $\geq$ 2 of 5 and $\geq$ 3 of 7 symptoms were needed from the respective categories at duration of $\geq$ 1 month and which caused the subject clinically meaningful functional impairment to attain a diagnosis of life time PTSD. Functional impairment was assessed by three questions which refer to help seeking behaviour, being upset at themself for the way the trauma made them feel and social and work avoidant behaviours. The current work also employed partial PTSD (also explained in paper seven, chapter seven).

Major Depressive Disorders

The MDD section of the CIDI 2.1 begins with two screeners, of which one must be satisfied to proceed further, asking whether the respondent has ever experienced a period of two weeks or longer in which they (i) felt sad, empty or depressed, or (ii) lost interest in activities which were usually enjoyable. Subsequently, respondents were asked if they had experienced depressive symptoms related to (a) lacking energy; (b) significant appetite/weight gain/loss; (c) insomnia, terminal insomnia or sleeping too much; (d) moving very slowly or unable to stop moving which was noticeable to others; (e) feeling worthless or guilty without good reason and not due to the disorder; (f) difficulty concentrating, unable to pay attention to

television and books normally enjoyed, thoughts coming slowly or feeling indecisive; (g) thinking a lot about death, thinking, planning or attempting suicide. From each of these seven symptoms categories (for which some could be indicated by one of many questions), respondents had to have experienced four symptoms during the two week period nearly every day, in addition to experiencing significant social or occupational dysfunction, to receive a diagnosis. A final series of questions concerns the onset, recency, severity and recurrence of the symptoms, in addition to determining if diagnoses of anxiety ascertained in prior sections fell within the course of the depressive symptoms and if the depression followed the loss of a loved one.

Generalised Anxiety Disorders

The GAD section of the CIDI 2.1 also begins with two screener questions, for which one must be satisfied to proceed further, asking if the respondent has experienced a period of six months or longer in which they felt (i) worried tense or anxious about everyday situation such as work or family, or (ii) more worried than most people would in the situation they were in. A subsequent section confirms that the worry was excessive, occurred on most days and was not caused by another medical condition or associated with drug use. One question in this section also verifies that the individual found it 'difficult to stop worrying'. Next a list of 24 indicators are listed describing symptoms of feeling restless or on edge, fatigue, difficulty concentrating, irritability, muscle tension, and sleep disturbance, of which respondents had to experience at least four in addition to significant social or occupational impairment to receive a diagnosis.